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ARCHIVES OF SURGERY

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CLINICAL USE OF PENTOBARBITAL SODIUM AS A PREANESTHETIC AGENT

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CLEVELAND

Pentobarbital sodium, because of the rapidity with which sedation or hypnosis occurs after its oral administration and the short duration of its action owing to its rapid destruction in the body, appeared to be one of the most promising of the newer fixed hypnotics for preanesthetic medication from both an experimental (Fitch, Waters and Tatum;[1] Barlow, Duncan and Gledhill;[2] Kleindorfer, 1932) and a clinical standpoint (Lundy;[3] Wilcox;[4] Magill[5]). The marked relief from apprehensiveness and the practical absence of disagreeable associated actions, such as preoperative excitement and respiratory or circulatory depression when used in effective dosages, suggested a trial of this agent for surgical premedication in man.

The use of pentobarbital sodium in the surgical service of the University Hospitals was begun in April 1932. The procedures established by experience have become routine, and this type of premedication at the present time is administered in approximately 65 per cent of all surgical cases requiring premedication. The present report is based on more than 700 records of surgical anesthesia and a detailed study of 455 records chosen at random from the entire group. The age of the patients ranged from 3 months to 81 years. The nature of the operative procedures in the series studied, grouped as to region in terms of percentages of the total, are as follows: head, 3.55; face, 8.66; neck, 10.21; chest, 9.19; breast, 6.44; back, 1.78; abdomen, 18.43; pelvis, 22.87, and extremities 18.87. The data obtained are considered sufficient to

From the Department of Anesthesia, the University Hospitals and the Department of Pharmacology, the School of Medicine, Western Reserve University.

1. Fitch, R. H.; Waters, R. M., and Tatum, A. L.: Am. J. Surg. **9**:110, 1930.
2. Barlow, O. W.; Duncan, J. E., and Gledhill, J. D.: J. Pharmacol. & Exper. Therap. **41**:367, 1931.
3. Lundy, J. S.: Anesth. & Analg. **9**:210, 1930.
4. Wilcox, W.: Brit. M. J. **1**:266, 1931.
5. Magill, I. W.: Lancet **1**:74, 1931.

establish the effects of the pentobarbital-morphine premedication sequence as to dosage of the hypnotic in relation to age and sex, and the nature of anesthesia produced with different types of supplementary anesthetics in relation to the type of operation and postoperative reactions.

PROCEDURE

The premedication varied somewhat with the nature of the operation, condition of the patient and the supplementary anesthetic to be administered. The usual sequence (in 70 per cent of the series) was as follows: Pentobarbital sodium (1½ grains [0.09 Gm.]) was administered in a capsule on the evening preceding the operation in order to assure a restful night. The following morning, two hours before the scheduled time for the operation 1½, 2 or 3 grains (0.09, 0.12 or 0.18 Gm.) of pentobarbital sodium (the dose gaged by the age and condition of the patient and the surgical indication) was administered orally. One hour later an equal dose of pentobarbital sodium was given orally with morphine (⅙ grain [11 mg.]) and atropine (1/150 grain [0.4 mg.]) hypodermically. The total amount

TABLE 1.—*Anesthetic Supplements and the Frequency with Which They Were Administered*

Anesthetic	Number of Cases	Percentage of Series
None	2	0.44
Local	90	19.93
Local and nitrous oxide and oxygen	2	0.44
Local and nitrous oxide, oxygen and ether	3	0.66
Sacral	8	1.77
Ether (drop)	15	3.31
Ether (vapor)	16	3.55
Nitrous oxide and oxygen	24	5.33
Nitrous oxide, oxygen and chloroform	1	0.22
Nitrous oxide, oxygen and ether	294	65.27

of the hypnotic administered on the morning of the operation was 3 grains or less in 51.3 per cent and more than 3 grains (4½ to 9 [0.29 to 0.58 Gm.]) in the remaining 48.7 per cent of the patients. The optimal amount appears to be from 3 to 5 grains (0.3 Gm.). Patients subjected to operation on the thyroid gland or the gallbladder reacted better to large than to small doses. Full doses of morphine (¼ grain [16.2 mg.]) were administered, usually in combination with small doses of the hypnotic, only when indicated by the condition of the patient or by the nature of the surgical case. Approximately one half the patients who were to undergo operation on the breast and two thirds of those who were to undergo operation on the gallbladder were medicated with maximal doses of morphine.

The observations obtained with different doses of pentobarbital sodium with each type of supplementary anesthetic included: the pulse rate, the respiratory rate, and the blood pressure before and after premedication, during and after anesthesia, the duration of the operation and of the period of postoperative sleep (to return of consciousness); postoperative nausea; emesis, restlessness and the urinary findings both before and after the operation. The respective effects of morphine (⅙ grain) and of different doses of pentobarbital sodium and morphine (⅙ grain) on the respiratory minute volumes were determined for a small group. The patients were questioned during convalescence as to the presence or absence of amnesia and their general impressions. The anesthetic supplements and the frequency with which they were administered are shown in table 1.

The data were tabulated according to sex and type of operation, but differed so negligibly (with the exception of the gynecological, gallbladder, thyroid and cerebral groups) that all data with these exceptions are presented as a single group, and have been subdivided only as regards age, dosage of pentobarbital sodium and supplementary anesthetic. The main group includes all patients within the age limits of 18 and 60 years (fig. 1). The smaller groups include (*a*) ages below 18, (*b*) from 18 to 39, (*c*) from 40 to 59 and (*d*) more than 59 years (fig. 2). The data as illustrated in the figures represent medians, and with the exception of the time of operation and postoperative sleep (in hours) are expressed as percentage changes from the original normal observations.

OBSERVATIONS BEFORE OPERATION

On arrival at the operating room (following medication with the pentobarbital sodium-morphine sequence), 24 per cent of the patients were asleep, 68 per cent were drowsy, analgesic and uninterested in any procedure; the remaining 8 per cent showed some inebriation and moved slightly when disturbed. With a total dose of 6 (0.38 Gm.) or more grains of pentobarbital sodium patients were invariably asleep. Approximately 1 of 5 showed some conjunctival congestion which persisted for about one half hour. This reaction is probably comparable to the similar condition observed in acute alcoholism, and occurs with regularity in animals after intravenous injections of the barbiturates (Richter and Oughterson;[6] Barlow[7]).

Respiration.—The normal respiratory rate was unaltered by premedication. Individual observations varied within a range of ± 10 per cent (from one to two respirations per minute). The respiratory volume, measured with a Bohr gas-meter before and after medication, was reduced slightly by pentobarbital and morphine. The change noted was unimportant and was similar in magnitude to that occurring during sleep. Morphine alone in a dose of 1/6 grain occasionally slightly increased, but usually diminished, the minute volume from 3 to 5 per cent. Medication with pentobarbital (3 grains) and morphine (1/6 grain) resulted in a 2 to 7 per cent depression. Following medication with larger amounts of the hypnotic (6 grains) and morphine (1/6 grain), a decrease in the minute volume, from 8 to 16 per cent (median 10), was noted.

Pulse Rate.—The pulse rate varied within a range of ± 7.5 per cent of normal. The majority of changes noted occurred in patients medicated with 3 grains or less of the hypnotic, and probably indicate

6. Richter, H. G., and Oughterson, A. W.: J. Pharmacol. & Exper. Therap. 46:335, 1932.

7. Barlow, O. W.: Unpublished data.

a slight insufficiency of such doses. The median data indicate that a slight rise in pulse rate occurs after medication with morphine and pentobarbital sodium.

Blood Pressure.—The blood pressure in the majority of patients was unchanged. However, oscillations on either side of normal were

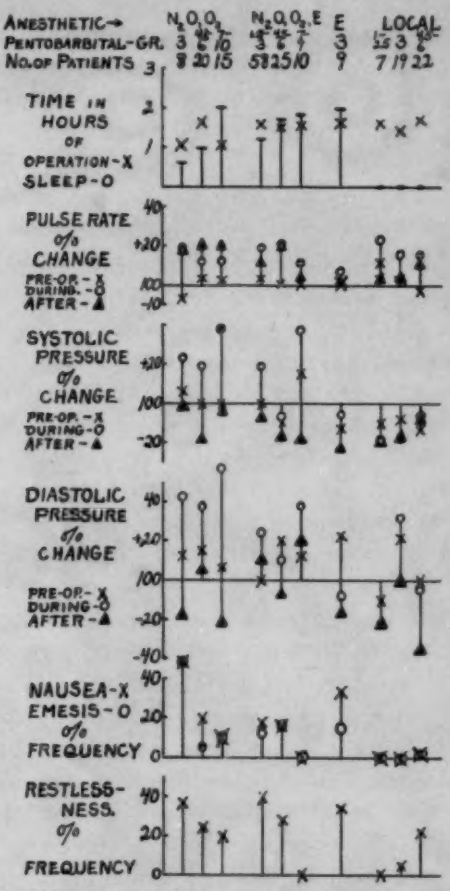
ANESTHETIC→ N_2O_2 $N_2O_2O_2E$ E LOCAL
PENTOBARBITAL-GR. 3 4½ 7½ 10 3 4½ 7½ 9 3 12 3 4½
NO. OF PATIENTS 3 8 20 15 5 8 25 10 9 7 19 22
TIME IN HOURS OF OPERATION-X SLEEP-O
A
PULSE RATE % CHANGE
PRE-OP.-X DURING-O AFTER-▲
B
SYSTOLIC PRESSURE % CHANGE
PRE-OP.-X DURING-O AFTER-▲
C
DIASTOLIC PRESSURE % CHANGE
PRE-OP.-X DURING-O AFTER-▲
D
NAUSEA-X EMESIS-O % FREQUENCY
E
RESTLESSNESS % FREQUENCY
F

Chart 1.—The data massed according to the anesthetic supplements that were used. In all the charts the symbols N_2O, O_2 N_2 O O_2 E, E and L at the top represent the anesthetic supplements nitrous oxide and oxygen, nitrous oxide, oxygen and ether, ether and a local anesthetic; the numbers in the second line the grains of pentobarbital sodium administered, and those in the third line, the number of patients whose anesthetic records are tabulated below.

observed, usually in conscious patients. If the patients were asleep, a decrease was noted. The degree of change was independent of the hypnotic dosage. Hypertensive patients usually showed the systolic change of sleep. The diastolic pressure was either unaltered or rose

with a median increase of from 3 to 7 per cent. The diastolic rise was most frequently observed in patients under 40 years of age, and a fall of from 5 to 10 per cent occurred in patients more than 59 years of age.

Nature of the Anesthesia.—Apprehensiveness on the part of the patient was rarely encountered following medication with pentobarbital

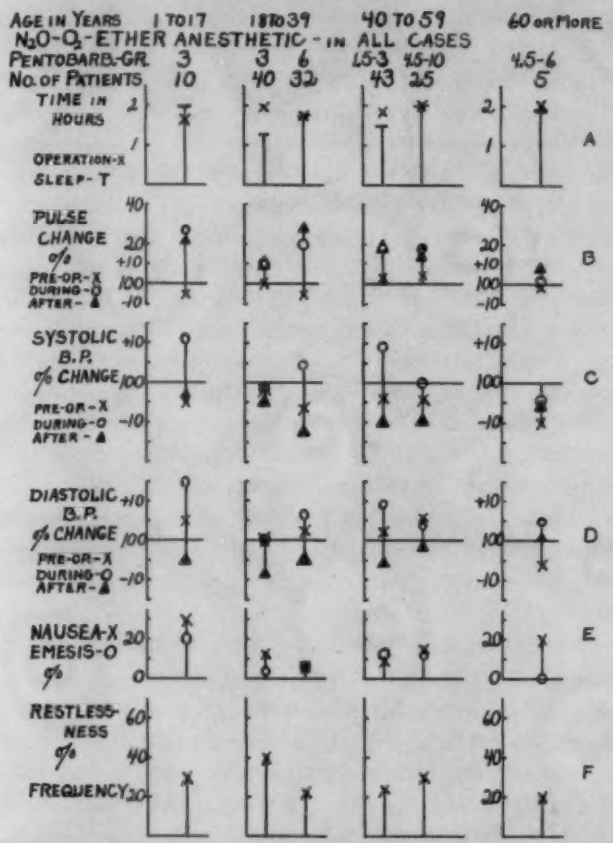

Chart 2.—The data massed according to the ages of the patients.

sodium (2 or more grains) and morphine.. The patients were asleep, uninterested in any procedure or cooperative. The period of induction was uneventful and independent of the nature of the anesthetic supplement. The quantity of the anesthetic required during the course of anesthesia was significantly less than that usually required with morphine and similar supplements alone. Surgical anesthesia was usually established within from three to six minutes and easily maintained. The most pleasing features of this anesthetic sequence are the ease of

establishment and maintenance of anesthesia, the wider margin of safety and the apparent absence of respiratory depression. With maximal doses of the hypnotic (from 6 to 9 grains), respiratory depression was observed exceptionally. Such reactions were due either to overmedication with morphine (½ grain) or to the condition of the patient, i. e., secondary anemia or a limited pulmonary surface. Under such conditions nitrous oxide and oxygen mixtures containing higher percentages of oxygen were sufficient to maintain good color as well as surgical anesthesia.

From 85 to 96 per cent of the anesthesias were good, the remainder fair. Poor anesthesias were infrequent (less than 0.5 per cent), but were most frequently observed with ether as the supplement. Anesthesias with nitrous oxide and oxygen, when preceded by the administration of morphine and pentobarbital sodium in doses of less than 3 grains, were somewhat less satisfactory than with from 3 to 4½ grains. So far as age was concerned, patients ranging from 1 to 39 years reacted equally well; i. e., anesthesia was satisfactory; it was somewhat less so with an age range of from 40 to 59 years and least satisfactory with aged patients (more than 59 years of age). Patients with gynecological or thyroid conditions (especially aged persons) reacted somewhat less satisfactorily than other groups to the premedication, gas-oxygen sequence. The degree of relaxation obtained in these two groups of patients was insufficient, necessitating the use of either maximal doses of pentobarbital sodium or the addition of ether to the nitrous oxide and oxygen mixture. Nitrous oxide, oxygen and ether was the anesthetic supplement of choice for the average patient.

OBSERVATIONS DURING AND FOLLOWING OPERATION

Changes in the Pulse Rate.—The median changes in pulse rate in the massed age group (from 18 to 60 years) observed preoperatively (after medication but preceding the administration of the supplementary anesthetic), during the course of anesthesia and on return to bed are illustrated (by symbols) in terms of the per cent variation from normal (100 per cent) in figure 1 *B*. Similar observations for different age groups are illustrated in figure 2 *B*.

Nitrous Oxide and Oxygen: The pulse rate increased from 15 to 27 per cent above normal during the course of anesthesia. The degree of rise was greatest with small to intermediate doses and least with maximal doses of pentobarbital sodium. The factor of dose does not appear significant, however. So far as age is concerned, patients ranging from 1 to 39 years reacted similarly. Minimal changes occurred in aged patients. Postoperatively, pulse rates fell slightly with small to medium doses, but rose above the operative peak with maximal doses. The postoperative pulse rate in immature patients (fig. 2) increased

maximally and corresponded closely to that noted with maximal hypnotic doses in adults.

Nitrous Oxide, Oxygen and Ether: With small doses of the hypnotic, the pulse rate increased to a smaller degree (fig. 1) than with nitrous oxide and oxygen. Only young patients proved an exception. The differences were not of great significance, however. With larger doses of the hypnotic no differences between the two supplements were apparent. Postoperatively the pulse rate as a rule fell slightly toward normal (except in aged patients, in whom a further rise occurred), and with maximal doses was within 5 per cent of normal.

Ether: Changes in the pulse rate in adult patients during ether anesthesia or postoperatively were unimportant. A negligible rise occurred as a rule. With young subjects receiving minimal doses of the hypnotic and fractions of the adult dose of morphine, the preoperative pulse rate increased 15 per cent, and an equal further rise occurred during anesthesia. This maximal level persisted postoperatively.

Local Anesthesia: The changes in pulse rate noted during local anesthesia were moderate, and bore no apparent relationship to the hypnotic dose, irrespective of age; but no change was apparent in the small group of immature patients on whom data are tabulated. Postoperatively the pulse rates fell toward normal, and with aged patients the terminal values were from 5 to 15 per cent below normal.

Blood Pressure.—During the course of anesthesia oscillations (especially postoperatively) were greatest in the aged, intermediate in the young and least in the average group. The qualitative change in preoperative systolic pressure bore no relation to the amount of hypnotic administered, and was increased, unchanged or decreased. A slight fall (from 2 to 5 per cent) was the rule, and differed negligibly as to age except in the aged, in whom changes were greatest. The oscillations observed may be attributed to individual variation or, more probably, to the relative physical state of the patients as reflected by their surgical requirements.

During the course of anesthesia, with all supplements except the local, the changes in systolic pressure were similar in direction, but quantitatively greater than the accompanying changes in pulse rate. With local anesthesia, the systolic pressure fell, but the degree of change was inverse to the rise in pulse rate. Postoperatively the pressure fell to or below normal, bore little or no relationship to the hypnotic dose or to the age of the patients, but increased with the several anesthestic supplements in the following order: nitrous oxide and oxygen, nitrous oxide, oxygen and ether, local, and ether.

The diastolic pressure varied preoperatively from a slight fall to a 20 per cent increase; the general picture as indicated by the median

reaction was a 10 per cent increase. The changes noted were unrelated either to the age of the patients or to the degree of premedication. During the course of anesthesia with either nitrous oxide and oxygen or nitrous oxide, oxygen and ether, the general blood pressure increased, but the diastolic change was greater than the systolic, owing probably to the moderate anoxemic factor. Under ether anesthesia the fall of the diastolic exceeded that of the systolic pressure. Under local anesthesia the oscillations were of greater magnitude than with other supplements. Postoperatively, the diastolic level fell from the values established during anesthesia to a level from 5 to 10 per cent below the preoperative figure. The degree of change was usually inverse to the degree of change which occurred during the course of anesthesia. No clearcut relationship could be observed between the degree of change and age, but the fall noted in the group receiving a local anesthesia was of greater magnitude than with the other anesthetic supplements.

Respiration.—Respiratory changes were unimportant. The rate was unaltered, although a slight decrease in volume occurred, as indicated by the minute volumes. During the course of anesthesia the respiratory rate increased from 30 to 60 per cent with a moderate compensatory decrease in volume. The changes observed differed insignificantly with the several anesthetics, except with the local anesthetics, with which a change of from 15 to 20 per cent occurred. The respiratory center was sensitive to carbon dioxide throughout anesthesia. Cyanosis occurred rarely and was not observed under conditions of proper premedication. The color of the patient was easily controlled by decreasing the percentage of nitrous oxide and increasing that of oxygen in the gas mixture. Aged patients showed a greater degree of depression and a smaller degree of stimulation during the course of anesthesia than younger patients. Postoperatively, respiratory rates and minute volumes returned either to normal or to the level of premedication sleep.

Duration of Postoperative Sleep.—The duration of postoperative sleep (solid line, section *A*, figs. 1 and 2) varied widely in individual patients, i. e., from a few minutes to ten hours. A rather remarkable variation existed in patients of comparable age, sex and general condition and subjected to the same operative procedure with the same premedication therapy. Lethargic persons invariably slept longer than excitable patients. The severity of the surgical procedures, the period of operation and the dosage of the hypnotic as well as the nature of the anesthetic supplement must be considered in explaining the observed variations in the time required for the return to consciousness postoperatively. The surgical procedures and the period of the operation as well as the narcotic dosage were for all general purposes constant, so that only the anesthetic supplements and the hypnotic need be taken

into consideration. The median time of sleep in the group receiving nitrous oxide and oxygen grossly parallels the dose of the hypnotic; i. e., with minimal doses the duration of sleep was forty minutes and with maximal doses two hours. With a nitrous oxide oxygen and ether supplement or an ether supplement the same order holds, but the differences with the three dosages of pentobarbital sodium are less significant. With these two supplements the additional postoperative depression caused by the ether per se was apparent, in that the time of sleep was shortest with nitrous oxide and oxygen, longer with nitrous oxide, oxygen and ether, and longest with ether, although the premedication was the same in each case. With local anesthesia the patients were rarely unconscious when they returned to their room. The absence of postoperative depression with local anesthesia is partly explained by the absence of additive depression from the hypnotic and anesthetic. In addition, the depression caused by premedication per se was probably diminished as a consequence of the known hypnotic-local anesthetic antagonism.

The amount of pentobarbital sodium required for the production of a unit reaction appears to be dependent, primarily, on the general condition of the patient and, secondarily, on age. For example, the youngest patient (3 months of age) in the series was medicated with 1 grain of pentobarbital sodium, while a 50 year old patient weighing more than ten times as much as the infant received 3 grains. Both patients were subjected to the same supplementary anesthetic and surgical procedures with equally satisfactory results. The observed relation between the effectiveness of the hypnotic and age, as indicated by the period of postoperative sleep is illustrated in figure 2. The order of sensitivity from greatest to least was: ages 1 to 17, 60 years or more, from 40 to 59 years and the group from 18 to 39 years.

Restlessness.—A few patients of the group of more than 700 receiving surgical anesthesia medicated with minimal doses of pentobarbital sodium became somewhat excited on arriving at the operating room instead of being quieted. Such reactions were exceptional. These patients were less cooperative than is normal and responded less satisfactorily to local anesthesia. Such reactions may be corrected by the production of a slight analgesia with nitrous oxide. Postoperative restlessness occurred in a certain percentage of all types of patients (*F*, fig. 1). It varied in frequency of occurrence with the hypnotic dose administered, but particularly with the type of patient. Apparently the frequency was somewhat less with moderate than with light doses, and might have been entirely absent with large doses. With the exception of those receiving ether and local anesthetics, the degree and frequency of occurrence were inverse to the duration of postoperative sleep. The restless movements, when present, were purposeless, and ranged

in degree from barely perceptible to marked movements which required at times either individual care for a few hours or, rarely, actual restraint. Morphine administered postoperatively was required by approximately one half of the restless patients and effectively controlled the reaction. Patients in the gynecological, thyroid or gallbladder groups were more prone to show postoperative restlessness than patients undergoing other types of surgical procedure.

The frequency with which restlessness occurred during the post-anesthetic stage with different age groups is illustrated in section *F*, figure 2. Athetoid movements were most frequent in subjects under 18 years of age, decreased in frequency in succeeding age groups and were least frequently noted in aged patients. Correlation of restlessness with the nature of the supplementary anesthetic indicated that the order of frequency from greatest to least was: ether, nitrous oxide, oxygen and ether; nitrous oxide and oxygen, and local anesthesia. The reaction noted following pentobarbital sodium and local anesthesia differed in one respect from that noted with the other supplements. With nitrous oxide and oxygen, for instance, the frequency decreased with increasing doses of hypnotic, but with the local anesthetics restlessness was absent with minimal doses and gradually increased with increasing doses of the hypnotic. Restlessness occurred exceptionally after the administration of the hypnotic-local anesthetic sequence in the age group of from 3 to 50 years, but occurred in 40 per cent of patients 60 or more years of age.

Nausea and Emesis.—These occurred postoperatively in all groups receiving supplementary anesthetics with the exception of those receiving local anesthesia. It appears therefore that pentobarbital sodium, independent of the dose, does not produce nausea or vomiting. Emesis occurred less frequently than nausea, but occasionally a small amount of mucus was vomited in the absence of nausea. The frequency of occurrence, although significantly less than that reported by Shaw,[8] was highest with ether, and apparently decreased with the other supplements as well as with increasing doses of the hypnotic. The frequency was somewhat greater in the group receiving nitrous oxide and oxygen than in those receiving nitrous oxide, oxygen and ether. This apparent paradox is unexplained, but may be related to the duration of post-operative depression. So far as age was concerned (fig. 2), the frequency of occurrence of nausea and emesis was greatest in the extremes of age and least frequent in the group from 18 to 39 years.

Urinary Findings.—Albumin was demonstrable in approximately 10 per cent of the first postoperative specimens, either voided spontaneously or obtained by catheter, and unless present on admittance disappeared after the first convalescent day. The majority of the

8. Shaw, R. W.: Lancet **2**:1435, 1932.

patients were females and less than one third of the specimens were obtained by catheterization. It is probable therefore that albuminuria occurs less frequently than these data indicate, as less than 4 per cent of the specimens of urine from males were positive for albumin postoperatively. Casts were rarely observed postoperatively, and when present were likewise noted preoperatively. The output of urine was reduced proportionately to the intake of water. Retention was apparently uninfluenced by the sequence of premedication used.

Period of Amnesia.—Complete amnesia occurred for from 5 to 8 hours postoperatively in approximately one third of the patients premedicated with 3 grains or less of pentobarbital sodium. The amnesia began from ten to thirty minutes after the administration of the capsule. Amnesia was partial; i. e., the memory was confused, in an additional 30 per cent. No amnesia was observed in the remaining 40 per cent. With larger doses of the hypnotic (4½ or more grains) amnesia was complete in 75 per cent of the patients and persisted for from nine to twelve hours and, exceptionally, for from eighteen to twenty-one hours postoperatively with maximal doses. The remaining 25 per cent had an imperfect memory for a period of several hours postoperatively. Following medication with from 9 to 10 grains (0.64 Gm.) of the hypnotic it was difficult to arouse the patients, who slept from eight to sixteen hours after being returned to bed.

The patients medicated with the hypnotic-narcotic-supplementary anesthetic sequence were pleased, having no disagreeable after-impressions, and being oblivious to any reactions that might occur in the postoperative period. From the standpoint of the patients, the most pleasing supplementary anesthetics were nitrous oxide and oxygen and a local anesthetic. Ether was least satisfactory.

OBSERVATIONS ON SPECIAL SURGICAL GROUPS

Nature of the Anesthesia.—The course of anesthesia was somewhat less satisfactory in patients in the thyroid and gynecological groups than in other surgical groups, in spite of heavy premedication with pentobarbital sodium. Poor anesthesias were more frequent, and greater difficulties were encountered in maintaining an even anesthesia. For the average patient who was to undergo an operation on the thyroid gland, the optimal premedication sequence appeared to be pentobarbital sodium, from 6 to 7½ grains, morphine, ⅙ grain, and atropine, (1/150 grain). Nitrous oxide and oxygen constitutes a satisfactory supplement. Aged patients responded less satisfactorily, however. The optimal premedication dosage for patients in the gynecological group appeared to be from 3 to 4½ grains of the hypnotic. Poor anesthesias were somewhat more frequent with heavier premedication, but postoperative reactions were less frequently observed after large than after

small doses of the hypnotic. Patients undergoing operations on the gallbladder responded best to from 6 to 7½ grains (0.48 Gm.) of pentobarbital sodium, followed by morphine, (¼ grain), supplemented with nitrous oxide, oxygen and ether. Aged patients responded especially well to this combination. With smaller doses of the hypnotic and full doses of morphine, anesthesia was least satisfactory. The efficiency of ether preceded by from small to moderate doses of the

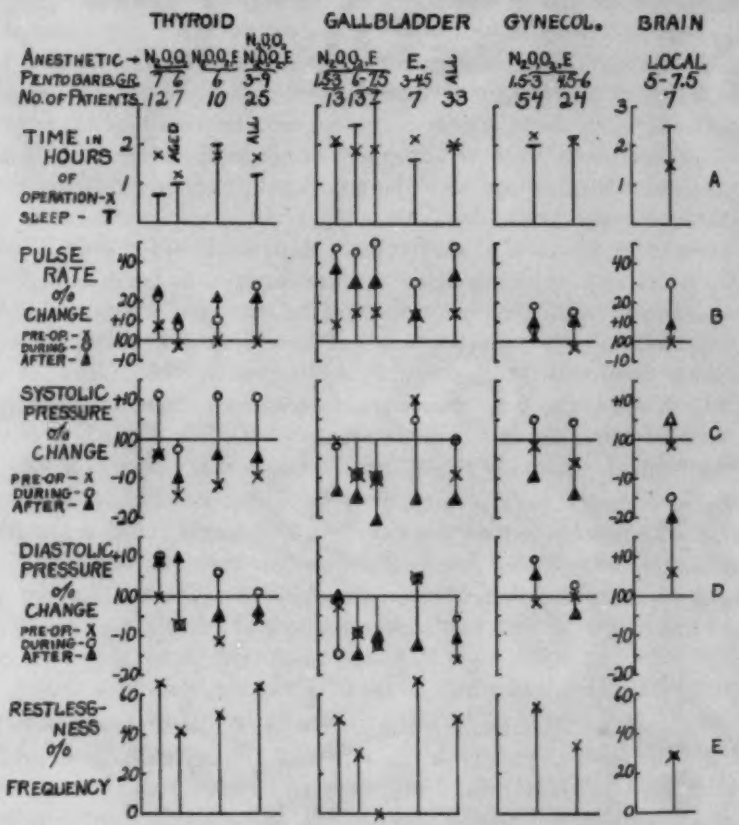

Chart 3.—The data on four special surgical groups, massed according to the types of surgical procedures involved.

hypnotic was intermediate between the two gas anesthetics used. The reaction of patients in the cerebral group to large doses of pentobarbital sodium and local anesthesia was excellent.

Pulse Rate.—The changes in pulse rate (fig. 3) noted preoperatively were insignificant in the thyroid, gynecological or cerebral groups. A 14 per cent rise was noted in the cholecystectomized group. During the course of the anesthesia or postoperatively, oscillations of the pulse

were of no greater magnitude than described for the general type of case (fig. 1). Oscillations were significantly greater in the group undergoing operation on the gallbladder than in any other type of case. During the course of the operation the pulse rate increased from 30 to 50 per cent and remained from 15 to 35 per cent above normal postoperatively.

Blood Pressure.—The blood pressure was little altered following premedication, although a decrease of approximately 10 per cent was noted with maximal doses. Systolic and diastolic changes were parallel. Occasionally a marked fall in blood pressure occurred which might have been due to individual susceptibility, in which case the dosage would probably have little influence. Such falls are so exceptional that the reaction should not limit the use of the method, especially, as it is not certain whether they were due to the drug or to some other unrecognized cause.

Respiratory Changes.—The changes observed in the special surgical groups did not differ significantly from those described for the massed group. The patients in thyroid and gallbladder groups although medicated with maximal doses of the hypnotic, as well as with full doses of morphine in the latter group, showed no greater alterations in the respiratory rate than were observed in other surgical groups. Patients in those groups appeared most resistant or tolerant to heavy premedication.

Period of Postoperative Sleep.—Patients with hyperthyroidism recovered consciousness more rapidly than any other type of surgical patient. Aged subjects recovered somewhat less rapidly than those in the age range of from 30 to 45 years. The duration of sleep differed significantly with different anesthetic supplements; i. e., with similar premedication postoperatitve sleep was at least twice as long with nitrous oxide, oxygen and ether as with nitrous oxide and oxygen. Patients with gynecological and gallbladder diseases slept somewhat longer than other surgical groups (with the exception of the brain group), owing probably to the greater severity of the surgical procedures. The long sleep following operations on the brain (in the absence of morphine) was in contrast to the reaction of other groups medicated with the hypnotic local anesthetic sequence, since, with the exception of the brain group, the period of postoperative sleep was rarely noted as independent of the hypnotic dosage.

Restlessness: Postoperative restlessness occurred in 64 per cent of the lobectomized group of patients. The frequency bore little relation to the hypnotic dose, but this reaction was more frequent following nitrous oxide and oxygen than after nitrous oxide, oxygen and ether. The lesser frequency together with the longer period of postoperative sleep with the latter supplement suggests that restlessness bears some

relation to the degree of postoperative depression. The high metabolic rate and nervous instability of such patients are probably of greater importance, however. Patients with gallbladder conditions were somewhat more restless than the general average, especially with small doses of the hypnotic. The frequency of restlessness decreased with increasing doses of the hypnotic, and none was noted in the aged group of patients.

The use of ether as the anesthetic supplement appeared to exaggerate the frequency with which restlessness occurred after comparable doses of the hypnotic and the other supplements. Patients in the gynecological group were somewhat more troublesome than those in other surgical groups from the standpoint of nursing. The data suggest that the dose of the hypnotic was insufficient, the major portion of the patients having received 3 grains or less. In this group restlessness was frequent. With larger doses (from 4½ to 6 grains) the factor of restlessness was no greater than in other surgical groups. This hypothesis appears substantiated in that postoperative restlessness has become relatively unimportant since pentobarbital (acid) was substituted for the sodium salt of the same preparation in the gynecological service. The lower frequency of postoperative movements noted after medication with the acid form of the hypnotic indicates that the dosage used previously was insufficient (the molecular weight of the acid is 10 per cent less than that of the sodium form) or that a longer postoperative depression occurs with the premedication sequence used at the present time. This point is being studied.

Nausea and Vomiting.—Nausea was recorded in 11 per cent of patients following thyroidectomy but emesis did not occur. The frequency was greater following the use of a nitrous oxide, oxygen and ether supplement. From 10 to 18 per cent of the gynecological patients were nauseated, and less than 10 per cent vomited postoperatively. Nausea did not occur in the group but emesis was observed in 1 case. The gallbladder group differed from the other group, in that nausea was much more frequent. The frequency with which nausea occurred bore little relation to the dose of the hypnotic, and, contrary to experience in all other surgical cases, was more frequent in the aged than in the younger patients. The frequency was four times as great after ether than after nitrous oxide, oxygen and ether, even though the premedication sequence was constant. Emesis occurred one-half as frequently as nausea. The greater frequency with which nausea and emesis occurred in the gallbladder series was probably related to the nature of the organic disturbance.

Urinary Findings: Changes following anesthesia were unimportant. The urinary findings in the cerebral group of patients were negative. No casts were observed in the urine of the gynecological group, and, although transient albuminuria was occasionally observed (in the first postoperative specimen only), the data are of negative value only, owing

to the infrequency with which catheterized specimens of urine were obtained. The presence of albumin and casts was noted much more frequently (normal specimens) in the thyroid and gallbladder groups, and especially in aged patients, than in the other groups. The frequency of the occurrence of casts was the same both preoperatively and postoperatively. The frequency and degree of albuminuria postoperatively were exaggerated temporarily by anesthesia, but it is improbable that premedication procedures contributed to the temporary renal changes noted.

EXCEPTIONAL REACTIONS IN ALL TYPES OF SURGICAL CASES

Unsatisfactory reactions of greater or less severity were noted in 3 per cent of the total number of case records studied in detail. These reactions were of three types: (1) a moderate fall in blood pressure during the preoperative period, (2) a moderate to severe fall in blood pressure during the course of the operation or during the postoperative period and (3) respiratory disturbances during the course of anesthesia.

The average fall of blood pressure in the first group, i. e., after medication but preceding the administration of the anesthetic, was 30 mm. of mercury. The pulse rate and respiratory rate were not significantly altered in 4 of the 5 patients included in this group. Four of the 5 subjects had been medicated with pentobarbital sodium (4½ grains), morphine (⅙ grain) and scopolamine ($\frac{1}{150}$ grain). The preponderant frequency with which reactions of this type occurred in the presence of scopolamine does not appear to be a coincidence, since reactions occurred in 20 per cent of all patients similarly medicated. The use of scopolamine in the presence of pentobarbital sodium and morphine is certainly of questionable value. Three of the 5 patients were treated with ephedrine (¾ grain) during the course of the operation. The patients were returned to bed on conclusion of the surgical procedures in good condition.

The second type of reaction, i. e., fall in blood pressure during or immediately following completion of the operation, was observed in 4 patients. The degree of change was insufficient in 2 cases to require treatment, but the other 2 patients showed signs of surgical shock. Satisfactory recoveries occurred in both patients following the administration of ephedrine in one and an infusion of dextrose intravenously in the other.

Three patients showed respiratory disturbances during the course of anesthesia. The first patient became cyanotic shortly after anesthesia was established, owing to faulty induction. Caffeine sodium benzoate was administered. The subsequent anesthesia was uneventful, and in spite of a long pelvic operation the patient was returned to her room in good condition. In a second patient, the induction of anesthesia with the usual nitrous oxide and oxygen mixtures was followed shortly by

marked cyanosis. This patient had received premedication with pentobarbital sodium (6 grains), morphine (⅙ grain) and atropine (1/150 grain). The reaction was considered due to the more than average sensitivity of the subject to morphine, i. e., to overmedication with the narcotic in the presence of large doses of the hypnotic. Similar reactions following the administration of sodium amytal and morphine under comparable conditions have been reported clinically by Fitch and his co-workers [1] and Zerfas [9] and observed experimentally by Barlow. The third patient had severe secondary anemia and became cyanotic during the course of anesthesia with nitrous oxide and oxygen. The last 2 patients received no treatment other than an increase in the percentage of oxygen in the gas mixture. The cyanosis was relieved without altering the character of the anesthesia.

Pulmonary Complications.—Following the use of the pentobarbital sodium-morphine general anesthetic sequence, pulmonary complications

TABLE 2.—*Complications*

Anesthetic Sequence	Number of Cases	Complications	Pulmonary Complications, per Cent of Series
Pentobarbital sodium and morphine, supplemented with nitrous oxide and oxygen, nitrous oxide, oxygen and ether or ether	378	1	0.26
Morphine and atropine, supplemented with nitrous oxide, oxygen and ether	505	11	2.18
Ether	185	5	2.7
Spinal	46	3	6.5
Spinal and nitrous oxide, oxygen and ether	8	2	25.0
Local anesthetic	341	3	0.88

were significantly less frequent than with other types of anesthesia. The frequency with which complications were observed during 1932 in a carefully controlled group of patients in the general surgical service is indicated in table 2. The data appear clearcut. We believe, however, that in view of the small total number of pulmonary complications noted the figures must be supplemented or confirmed before this point can be definitely established.

SUMMARY AND CONCLUSIONS

The present report is a review of the records of more than 700 surgical anesthesias in which the patients received premedication with pentobarbital sodium in doses ranging from 1½ to 9 grains (optimal, from 3 to 4½), morphine and atropine supplemented with several types of general anesthetics.

9. Zerfas, L. G.: Brit. M. J. **2**:897, 1930.

Preanesthetic medication with pentobarbital sodium and morphine reduces or eliminates apprehensiveness so that the patient with rare exceptions arrives in the operating room either asleep (depending on the hypnotic dose administered and the relative sensitivity of the patient) or wholly uninterested in any mechanical or anesthetic procedure. The pulse may be unchanged or may oscillate on either side of normal, but an increase of from 1 to 4 per cent occurs as a rule. The changes in blood pressure and pulse rate preoperatively bear an inverse relation; i. e., a rise in the pulse rate is usually coincident with a slight decrease in the blood pressure. The median variation in blood pressure is within a range of plus or minus 7 per cent. The circulatory changes observed following premedication were not significantly divergent in different surgical types with the exception of patients with thyroid and gallbladder conditions. In the two exceptional groups oscillations were more variable and slightly greater in degree. The respiratory rates were unaltered by premedication. The respiratory volume as indicated by recorded changes in the minute volume was reduced insignificantly, and the decrease noted even with maximal doses of the hypnotic (and narcotic) was within the normal range of changes occurring during sleep.

The induction of anesthesia was smooth, distinctly shorter in point of time than in the absence of the hypnotic, and anesthesia could be established and maintained with ease with smaller quantities of the supplementary anesthetic than are required without such premedication. From 85 to 96 per cent of the anesthesias were good; the remainder were "fair." Poor anesthesias were infrequent. Anesthesias were least satisfactory in patients in the thyroid and gynecological groups. The hypnotic-narcotic-supplementary anesthetic sequence was most satisfactory in young and least satisfactory in aged patients. Nitrous oxide, oxygen and ether was the supplementary anesthetic of choice.

The pulse rate increased from 10 to 20 per cent during the course of anesthesia, and diminished somewhat from the operative peak immediately following the period of anesthesia. Changes in the pulse rate were maximal in young and minimal in aged patients; the changes observed in patients with surgical conditions of the thyroid and gallbladder were of greater magnitude than in other surgical types.

The blood pressure varied widely in exceptional cases during the course of operation, i. e., from 10 per cent below to 25 per cent above normal. In general, a rise of from 5 to 10 per cent above normal was observed with nitrous oxide and oxygen or nitrous oxide, oxygen and ether. With ether or local anesthesia the median pressure either decreased or increased slightly from the premedication level but, with the exception of the group undergoing operations on the brain, it remained below normal during the course of the operation. Systolic

and diastolic pressures, although qualitatively similar, differed markedly in exceptional instances. Postoperative pressures fell somewhat from the levels established during anesthesia.

Respiratory values during the course of anesthesia were difficult to evaluate. The rates increased significantly, and a moderate compensatory decrease in volume was observed. Disturbances were rare, and when such reactions occurred, were corrected by the adjustment of the anesthetic mixture of nitrous oxide and oxygen. Postoperatively, the respiratory rates and volumes returned either to normal or to the preoperative values.

The duration of postoperative sleep, although obviously influenced by the severity of the operative procedures to which the patients were subjected and the nature of the general anesthetic used, showed a fairly close correlation with the nature of the patient, i. e., with the general condition, metabolic level and nervous stability. Excitable persons (especially those with abnormal thyroid glands) require heavier premedication for a unit reaction than do lethargic patients. Body weight, according to this study, bore little relation to the degree of reaction of similar age and surgical groups to the same medication. No sexual differences were discernible. Age appears to be of some importance so far as the reaction to a unit dose is concerned. The observed susceptibility as judged by the duration of sleep postoperatively (type of operation and anesthetic being constant) appears to be in order from greatest to least: the immature age group (from 1 to 18); the aged (60 or more years), the 40 to 59 year group and least in the group from 19 to 39 years of age. The margin of safety appears wide, but caution should be observed if more than 9 grains is given, even with the sequence of divided doses used, and especially in the presence of morphine. Patients medicated with 9 to 10 grains are difficult to arouse; they sleep from eight to (exceptionally) sixteen hours postoperatively. Respiratory disturbances occur more frequently with maximal doses of the hypnotic in the presence of morphine, and occasionally the maintenance of a satisfactory color necessitates an increase in the percentage of oxygen in the gas mixtures as ordinarily used. Under such conditions the depth of anesthesia is uninfluenced by the accompanying decrease in the nitrous oxide in the mixture.

Purposeless movements ranging in severity from those just discernible to those requiring restraint were observed postoperatively in from 20 to 45 per cent of the patients medicated with pentobarbital sodium. The frequency was greatest in young and least in aged patients and decreased significantly with increasing doses of the hypnotic. Such movements may be entirely absent with maximal doses. Patients who had an operation on the thyroid or gallbladder were more restless postoperatively than other surgical types. Morphine effectively controlled these reactions.

No renal effects of the premedication sequence were noted. Any changes observed were easily explainable as minor reactions to the supplementary anesthetic and operative procedures, and in the main compared closely with preoperative findings.

The effectiveness of premedication with pentobarbital sodium appeared to be distinctly improved, especially as to the analgesia obtained, by the addition of small doses of morphine. Large doses of the hypnotic appear to be indicated in lobectomies and cholecystectomies. In the latter group full doses of morphine (¼ grain) are indicated in addition. In general, full doses of morphine should be used cautiously when more than 5 grains of pentobarbital sodium have been administered owing to occasional sensitivity of patients and the greater tendency of such medication to cause respiratory depression.

Amnesia beginning shortly after the administration of the hypnotic and persisting for from five to twelve or more hours postoperatively was observed in at least 75 per cent of the group of patients receiving 3 or more grains of pentobarbital sodium.

Undesirable reactions were observed preoperatively (before the administration of the anesthetic) in 5 cases and during or postoperatively in 7 cases. The preoperative change was a fall of blood pressure usually of moderate degree, although in 1 case the pulse became imperceptible. Four of the 5 patients received pentobarbital sodium, morphine and scopolamine. Three were treated with ephedrine during the course of the operation, but all were returned to bed in good condition. During the course of or following anesthesia a moderate to severe fall in blood pressure occurred in 4 patients. Two were in a state of shock and required treatment. Cyanosis was observed in 3 patients during the course of anesthesia, owing to improper medicatjon for their physical condition. Operative procedures were not interrupted, and the color was controlled by increasing the percentage of oxygen in the mixture of nitrous oxide and oxygen.

GAS BACILLUS INFECTION COMPLICATING LAPAROTOMY

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It is the purpose of this report to draw attention to gas bacillus infection [1] following laparotomy; this condition is manifested by a fulminating clinical course which may terminate fatally with startling rapidity. Failure to think of this complication, and the consequent omission of pertinent bacteriologic studies, may leave the surgeon mystified as to the actual cause of death. Frequently it is only when a postmortem examination is performed that the situation is clarified.

Winter,[2] in 1889, reported 2 cases in which emphysema of the abdominal wall occurred after laparotomy. Eight years later Russell [3] reported 2 similar cases: one after uterine suspension and the other following a panhysterectomy. Subsequently, several reports of cases appeared in which gas gangrene was described as a complication of abdominal operations. It was reported after cholecystectomy, gastric and colonic resection, enterostomy and closure of a perforated peptic ulcer. However, the majority of infections with the gas bacillus occurred after appendectomy for gangrenous appendicitis.

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1. The gas bacillus, a frequent inhabitant of the intestinal tract, has been studied extensively in its relation to gangrenous appendicitis. Eleven cases of gas bacillus infection following operation for gangrenous appendicitis were reported by Simonds (Studies in Bacillus Welchii, New York, Rockefeller Institute, 1915). Bier (Ann. Surg. **81**:1117, 1923) and Ochsner and Schmidt (S. Clin. North America **5**:911, 1925) each reported a case of gas bacillus infection of the abdominal wall following appendectomy, with recovery. In 139 cases of appendicitis gas bacilli were isolated in 49 of the diseased appendixes, by Lanz and Tavel (quoted by Jennings: New York M. J. **117**:682, 1923). Hyde and Frederick (quoted by Jennings) found gas bacilli in 100 of 102 cases of acute appendicitis. Grigeroff (quoted by Russell [3]) noted that in normal appendixes, the aerobes and anaerobes were in equal proportions, or the aerobes predominated, whereas, in inflamed appendixes the strictly anaerobic bacilli were strikingly predominant. It is probable that the anaerobic gas bacilli take a significant part in the development, if not the causation, of acute appendicitis.

2. Winter, quoted by Russell.[3]

3. Russell: W. W.: Postoperative Emphysema of the Abdominal Wall, Am. J. Obst. **35**:517 (April) 1897.

Despite the widespread prevalence of the anaerobic bacilli, gas bacillus infection following laparotomy is relatively rare. The organisms have been identified in the discharge from abdominal drainage tracts, especially in cases of gangrenous appendicitis and acute cholecystitis. The gas bacillus has been isolated from the biliary tract and liver immediately after death. Gordon-Taylor and Whitby [4] reported the finding of Bacillus Welchii in cases of severe cholecystitis and in gangrenous gallbladders. This organism was isolated in 9 per cent of their cases of acute cholecystitis. In the routine examination of gallstones taken at autopsy these authors found B. Welchii in the nucleus of 13 per cent of the calculi. In view of the lack of correlation between the occurrence of gas bacillus infection and the extensive distribution of the organism, it is apparent that special conditions must obtain for its inception and development.

As has been demonstrated by Andrews and Hrdina,[5] the introduction of a bit of sterilized liver tissue into the peritoneal cavity of a rabbit will result in a gas bacillus infection. Evidently the introduction or formation of proteolytic substances produces the necessary conditions for the activation of the gas bacillus. Apparently the virulence of the organism is considerably enhanced in the presence of necrotic tissue.[6] The autolysis of devitalized tissue high in protein content produces substances which favor the appearance and rapid growth of anaerobic gas bacilli. Extensive involvement has occurred, however, in cases in which the amount of necrotic tissue originally present was almost negligible. When contamination occurs, it is probably due to the malignant toxin of the gas bacillus which provides by its necrotizing action the dead tissue indispensable to the development of the gas bacillus infection. The muscle is killed by a toxin-bearing edema which goes ahead of the bacillus. The gas may be a factor in opening up new channels, but without a necrosis-producing toxin the infection could not advance. The relative avirulence of the toxin of certain strains of

4. Gordon-Taylor, G., and Whitby, E. H.: A Bacteriological Study of 50 Cases of Cholecystectomy with Special Reference to Anaerobic Infection, Brit. J. Surg. **18**:78, 1930.

5. Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, Surg., Gynec. & Obst. **52**:61 (Jan.) 1931.

6. Reith (J. Bact. **12**:367, 1926) reported the presence of B. Welchii in the muscular tissue of normal animals. Andrews, Rewbridge and Hrdina (Surg., Gynec. & Obst. **53**:176, 1931) studied the production of B. Welchii infections in dogs by the injection of sterile liver extracts or bile salts. They showed that abscesses were produced which yielded B. Welchii, and they expressed the belief that the organism was already present in the tissues. They found that when large quantities of ground muscle tissue were placed in the abdominal cavity of experimental animals, invariably a gas bacillus infection resulted. This usually did not occur if the muscle was not ground.

anaerobic bacilli accounts in part for the cases in which the patient recovers. Furthermore, the heterogeneity of the group also is partly responsible for the varied clinical aspects and the different responses to serum treatment. Clinically it has been noted that the presence of streptococci, staphylococci and Bacillus coli results in an increased virulence of B. Welchii. Meleney and his associates [7] demonstrated with mixtures of B. Welchii and the common pyogenic organisms that the lethal dose in mice was considerably smaller than that of each organism alone. They expressed the belief that a definite synergistic action occurs.

The infection may begin in the muscle of the abdominal wall, the peritoneal cavity or the liver. The pathologic changes are the result of the toxemia alone or of the toxemia plus the presence of organisms and gas. When muscle is involved it becomes edematous, necrotic and crepitant. The "cooked meat" appearance is typical. Microscopically the muscle bundles appear necrotic; the sarcoplasm is dense and contracted, producing a space between it and the sarcolemma. This space is said to contain the toxin-bearing edema. The gas is found mainly along fascial planes. The liver shows marked parenchymatous degeneration, true toxic hepatitis, which may progress to widespread necrosis. Toxic nephritis is present. A constant feature is the extensive necrosis of the suprarenal glands. Similar toxic changes exist in practically all the other viscera. When the gas bacilli circulate in the blood stream, a characteristic infiltration of all tissues by gas occurs. The liver has a spongy, foamy appearance. On sectioning the preserved, fixed brain reveals a "Swiss cheese" appearance. Tremendous infiltration of all the tissues by gas bacilli takes place. The air bubbles may even appear to be lined with gas bacilli.

The clinical picture is one of overwhelming toxemia. Within from six to twelve hours after operation certain alarming signs may appear in a patient whose postoperative recovery has been proceeding satisfactorily. The blood pressure begins to drop slowly but steadily, and the pulse rate is accelerated correspondingly. The anxious, restless patient becomes semistuporous and finally lapses into coma. The skin and extremities are pale, cold and moist. The most striking phenomenon is the progressive increase in body temperature, reaching sometimes as high as from 108 to 110 F. Despite the usual antipyretic measures, the temperature does not fall. The combination of very high fever and pale cold skin signifies an extreme degree of peripheral vasoconstriction. Shock therapy produces little or no improvement. Examination of the

7. Meleney, F. L.; Olpp, J.; Harvey, H. D. and Jern, H. Z.: Peritonitis: Synergism of Bacteria Commonly Found in Peritoneal Exudates, Arch. Surg. **25**: 709 (Oct.) 1932.

wound may give negative results; however, if the infection involves the abdominal wall, crepitation may be elicited early. There is a marked diminution of the urinary output; complete anuria may occur. This may be accompanied by a deepening jaundice, and the icteric index may rise to 100 or more. The nonprotein nitrogen of the blood increases without a corresponding rise in the blood urea nitrogen. The urine has a high specific gravity and contains albumin and casts. The white cell count ranges between 20,000 and 30,000 per cubic millimeter.

Of late the literature has contained many reports describing the clinical aspects of postoperative "liver deaths." Heyd,[8] in discussing this entity, described three distinct types, one of which was similar to the clinical picture existing in gas bacillus toxemia and septicemia. As an illustration he described a patient in whom, shortly after operation, the temperature rose sharply. The pulse and respiratory rates became rapid. The patient became comatose and died in thirty-six hours. The postoperative course of our patients with gas bacillus infection was practically identical with this description by Heyd. In case 2 the diagnosis of acute hepaticorenal insufficiency was made, and it was not until the postmortem examination that the true cause of death was ascertained. The nonprotein nitrogen of the blood and the icteric index had both risen rapidly. The blood urea nitrogen was elevated to a lesser degree. The urinary output for the entire postoperative course was 7 ounces (198 Gm.). The similarity in the clinical manifestations of gas bacillus toxemia and those of hepaticorenal insufficiency indicates that actually acute insufficiency exists as a result of gas bacillus toxemia. The liver and kidneys in all our cases showed extensive parenchymatous changes. It is conceivable that in some cases the element of hepaticorenal insufficiency may be primary, with the gas bacillus infection engrafted on an already necrotizing, degenerating liver. That this secondary infection is possible and probable has been conclusively demonstrated by Mason [9] and by Andrews and Hrdina.[5] Especially in the cases of hepaticorenal insufficiency following traumatic pulpefaction of the liver, such as those reported by Heyd and Schutz [10] and others, it would seem that conditions are exceedingly favorable for the development and appearance of gas bacillus infection. Other than acute hepaticorenal insufficiency there are few conditions which simulate gas bacillus toxemia and septicemia. An acute, fulminating, streptococcic septicemia will occasionally produce

8. Heyd, Charles G.: "Liver Deaths" in Surgery of the Gallbladder, J.A. M. A. **97**:1847 (Dec. 19) 1931.

9. Mason, E. C.; Davidson, E. C.; Matthews, C. W., and Rastello, P. B.: A Study of Tissue Autolysis in Vivo, J. Lab. & Clin. Med. **10**:622 (May) 1925.

10. Helwig, F. C., and Schutz, C. B.: A Liver-Kidney Syndrome, Surg., Gynec. & Obst. **53**:570 (Nov.) 1932.

hyperpyrexia and coma. Also, in the differential diagnosis, one must include the possibility of uremia, certain types of intracranial lesions and severe peritonitis. However, in each of these conditions characteristic features can usually be recognized.

Because of the rapid course of postoperative gas bacillus infection, early recognition is essential if any result is to be expected from treatment. At best, treatment of this distressing complication is disappointingly ineffective. Measures directed at lowering the temperature, combating the toxemia and supporting the circulation are indicated. Specific antitoxin should be given. Intravenous and subcutaneous infusions of large quantities of saline and dextrose solutions may be used in an attempt to offset the shock and toxemia. Concentrated solutions of dextrose are indicated because of the extensive damage to the liver and because of the need for a diuretic. There may also be some virtue in a 50 per cent solution of dextrose as an antipyretic agent. At the first suspicion of the presence of this complication, large doses of gas bacillus antitoxin should immediately be administered intravenously. The usual skin test for sensitivity should be performed. From one to four therapeutic doses of polyvalent antitoxin containing at least 10,000 units each of B. Welchii and vibrion septique antitoxin per dose should serve as the initial administration. An additional therapeutic dose should be given intramuscularly. The intravenous administration of antitoxin should be repeated every two to four hours during the crucial period. If crepitation is elicited in the wound, the sutures should be removed, the wound laid open and smears of the exudate taken. Free incisions may be necessary if the process is extensive. Hydrogen dioxide or surgical solution of chlorinated soda may be instilled into the wound at frequent intervals through Carrel-Dakin tubes.

When the infection involves the blood stream, peritoneum or liver, the outlook seems hopeless. The prognosis in cases of gas bacillus infection localized in the abdominal wall depends on the virulence of the particular bacterial strain, the severity of the toxemia and the resistance of the patient. The early institution of adequate treatment may be the deciding factor in the outcome. The mortality in any event will be discouragingly high. Death occurred in our 4 cases.

REPORT OF CASES

CASE 1.—M. S., a salesman, 40 years old, was admitted to the hospital on Oct. 19, 1932, complaining of loss of weight for one year. For fourteen months the patient had suffered intermittent attacks of acute epigastric pain followed by vomiting. There had been periods of constipation, with the passage of small black lumps after catharsis. His appetite became poor, and he became progressively weaker. He had lost 40 pounds (18.1 Kg.) during the previous twelve months.

Physical examination revealed a well developed, undernourished man, whose skin and mucous membranes were pale. The heart, lungs and abdomen were normal. The blood pressure was 110 systolic and 75 diastolic. Rectal examination gave negative results. The urine was normal. The blood count showed: red blood cells, 3,250,000; hemoglobin content, 50 per cent; white blood cells, 6,700, and the differential smear was negative. Stools showed occult blood on all examinations. The results of serologic tests were negative. Gastric analysis showed nothing remarkable. A barium sulphate enema showed a constant narrowing at the upper portion of the ascending colon, about 7 cm. in length, having the characteristic appearance of annular growth, probably carcinoma. Roentgenograms revealed no evidence of metastases.

On October 26, under nitrous oxide, oxygen and ether anesthesia, the cecum and ascending colon were resected, and an ileotransverse colostomy and enterostomy were made. The patient left the operating room in good condition. His temperature gradually rose, reaching 104.6 F. the day following operation. Simultaneously the pulse rate increased to 144, and the respiratory rate to 40. The abdomen was flat and soft. The enterostomy tube functioned well. The blood pressure gradually became lower. The total urinary excretion was only 3 ounces (84.9 Gm.). Dextrose and saline solutions were given without any effect. On the morning of October 28 the temperature was 110 F., the pulse rate 160 and the respiratory rate 40. The patient grew comatose and his blood pressure gradually became imperceptible. Stimulants were given, but to no avail. At 4 a. m. on October 28, the patient died. Two hours before death, examination of the abdomen revealed for the first time, crepitation about the enterostomy wound.

At postmortem examination, performed eight hours after death, subcutaneous crepitation could be felt over the right half of the abdominal wall. There was a foul serosanguineous discharge from the stab wound around the enterostomy tube. The muscles in this region were edematous, brown and crepitant. There was a small amount of turbid fluid in the peritoneal cavity. The spleen was soft, but of normal size. Gas bubbles could be expressed from its cut surface. The liver showed fatty degeneration. Bacillus Welchii was isolated from the abdominal wall. The suprarenal glands were necrotic. The presence of typical gas bubbles, surrounded by bacilli, was the prominent finding in the necrotic muscle of the abdominal wall.

Comment.—This case presented a fulminating toxemia from which the patient died thirty-six hours after operation. The ileostomy opening was undoubtedly the source of contamination with B. Welchii. The major features of the postoperative course were the hyperpyrexia and profound shock. The postmortem observations were typical.

Case 2.—A. M., a man, 56 years old, was admitted on July 19, 1932, complaining of severe pain in the right upper quadrant of the abdomen of twelve hours' duration. There had been two similar attacks during the three years before admission with no history of jaundice, clay-colored stools, nausea or vomiting.

Physical examination revealed marked tenderness and spasm in the right upper quadrant of the abdomen and a tender mass the size of an orange in this region, just below the costal margin. The edge of the liver was palpable 3 inches (7.6 cm.) below the costal margin. The temperature was 100 F. (rectal) and the blood pressure was 145 systolic and 90 diastolic. The urine was normal; the blood count showed: white blood cells, 11,600; red blood cells, 3,150,000, and hemoglobin content 70 per cent. The stools contained bile. The icteric index

was 12.5, the nonprotein nitrogen, 32, and the blood sugar, 95. The results of serologic tests were negative.

On July 21, cholecystectomy with drainage was performed under spinal anesthesia. Twenty hours after operation the temperature began to rise, and examination showed some abdominal distention. The patient became drowsy. The urinary output was 4 ounces (9.32 Gm.) in the twenty-four hours following operation, in spite of a fluid intake of 4,000 cc. Thirty hours after operation the patient became comatose, and showed an icteric tint. There was twitching of the muscles about the mouth. Three more ounces of urine was obtained by catheterization. The temperature gradually rose to 110 F. and persisted at this level. The icteric index increased rapidly, and the skin became cold and clammy. The blood pressure fell steadily, and there was an increasing weakness of the pulse. The nonprotein nitrogen was 110 mg. and the blood urea nitrogen, 46. Death occurred forty hours after operation. Postmortem examination revealed early purulent peritonitis. The liver showed extensive degeneration, and was markedly enlarged. On sectioning it gas bubbles were noted. Bacilli Welchii were recovered from its cut surface. The spleen and suprarenal glands showed marked necrosis. An acute toxic nephritis was present. The brain was swollen, and on sectioning, after fixation, showed a "Swiss cheese" appearance. Microscopically the organs showed parenchymatous degeneration associated with gas bubbles and bacilli.

Comment.—It is significant that the clinical diagnosis was hepaticorenal insufficiency. This is not surprising in view of the presence of hyperpyrexia, coma, urinary suppression, jaundice and evidence of nitrogenous retention. This case illustrates the similarity between gas bacillus toxemia and septicemia and hepaticorenal insufficiency, and suggests that the element of hepaticorenal insufficiency is actually present in severe gas bacillus toxemia.

CASE 3.—C. D., a woman, 67 years old, was admitted on Jan. 19, 1933, complaining of recurrent attacks of sharp pain in the right upper quadrant and in the epigastrium during nine months before admission. One month before admission she had a severe attack associated with chills and fever. Three weeks before entry she noticed jaundice, which became progressively deeper. Following the onset of the jaundice the urine became dark and the stools clay-colored. The patient gave a history of a loss of 10 pounds (4.5 Kg.) during the month before admission.

Physical examination revealed marked jaundice; the temperature was 100.2 F.; the blood pressure was 150 systolic and 70 diastolic; the abdomen was prominent; the edge of the liver, somewhat tender, could be felt about one handbreadth below the costal margin. The urine contained: albumin, a slight trace; bile, 4 plus. Repeated examinations of stools revealed no bile. The red blood cell count was 4,100,000; the hemoglobin content 60 per cent; the white blood cell count, 7,500, the differential smear, normal; nonprotein nitrogen, 24 mg.; the bleeding and clotting time normal, and icteric index, 150.

The patient was prepared for operation with intravenous injection of solutions of dextrose and calcium chloride. On January 25, under spinal anesthesia, the abdomen was explored. The gallbladder was dilated, and the head of the pancreas was definitely thickened. Cholecystogastrostomy was performed.

Twelve hours after operation the temperature rose to 104 F. and the pulse rate to 140. Catheterization at this time yielded 2 ounces (58.6 Gm.) of urine. Eighteen hours postoperatively the temperature was 106 F., the pulse became almost imperceptible, and the blood pressure dropped to 75 systolic and 40 diastolic. The patient rallied slightly after an intravenous infusion of 500 cc. of a 10 per

cent solution of dextrose. Examination of the wound revealed no evidence of crepitation, but the abdomen was tense in its upper half, and there was more tenderness present than was expected. Twenty-four hours after operation the patient was in a comatose state; at this time she was completely anuric. The nonprotein nitrogen was 45 mg. Despite the administration of large amounts of fluids by clyses and concentrated dextrose intravenously, the patient failed to excrete any urine. Thirty-six hours postoperatively the temperature rose to 109 F., the pulse was not perceptible and the patient died in spite of all treatment.

At postmortem examination extensive parenchymatous degeneration of the liver, kidneys and suprarenal glands was found. The liver, on section, was seen to contain numerous gas bubbles, and B. Welchii was isolated from its cut surface. The pancreas showed chronic inflammation.

Comment.—The profound toxemia and rapidly fatal termination illustrate the typical manifestations of gas bacillus infection.

Case 4.— E. E., a woman, 37 years old, a kitchen worker, was admitted on April 14, 1930, complaining of diarrhea, headache and abdominal pain. For six days previous to admission there had been from ten to twelve watery brown stools each day. Three days before admission the patient had chills, fever, general malaise and sweats. There was generalized pain in the lower part of the abdomen.

The physical examination revealed: evidence of consolidation at the base of the left lung, and the abdomen, markedly protuberant, contained a large fluctuant tumor. The temperature was 104 F. (rectal); the pulse rate 110; the respiratory rate 25; white blood cells 22,000, and the urine normal. While under observation the temperature continued to be elevated, up to 103 F., and there was persistent leukocytosis. The Widal test gave negative results. The stools decreased to two a day. Blood cultures were negative. Ten days after admission the patient complained of burning micturition. Examination revealed a large abdominal tumor completely filling the pelvis. This was very tender, and the uterus could not be felt. The diagnosis of ovarian cyst with possible malignant degeneration was suspected.

On May 15, under spinal anesthesia, laparotomy was performed. Two large tubo-ovarian masses, the size of footballs, filled the abdomen. The left was larger than the right, and both masses seemed to contain foul, purulent material. The abscesses were broken into and the masses were removed with considerable difficulty. During the operation, a small opening was inadvertently made in the sigmoid flexure; this was immediately sutured. The patient was given an intravenous infusion of dextrose immediately following operation, and was returned to the ward. Late in the afternoon she showed evidence of shock; treatment by fluids administered intravenously and transfusion did not improve the condition, and the blood pressure continued to fall. The temperature rose to 107 F. and the pulse to 160. Despite this pyrexia, the skin was cold, moist and clammy. The patient lapsed into a coma, her respirations became irregular, and she died sixteen hours after operation.

The postmortem examination disclosed widespread peritonitis with walled-off pockets of foul-smelling pus. There were hemorrhagic pleuritis and pericarditis. Throughout the myocardium were small gas bubbles. The spleen was enlarged, congested and crepitant. The liver presented a typical foamy appearance. Microscopic sections revealed a widespread distribution of gas bubbles. At the periphery of the bubbles were numerous bacilli. Bacilli Welchii were cultured from the

heart, spleen and lungs. Extensive parenchymatous degeneration was present in the liver and kidneys. The suprarenal glands were almost completely necrotic.

Comment.—This case presents the picture of overwhelming toxemia and septicemia, from which the patient died within sixteen hours of operation. The accidental opening of the intestine was probably the mode of entrance of the bacteria. The major feature of the postoperative course was the hyperpyrexia associated with the clinical evidence of surgical shock.

SUMMARY

Gas bacillus infection as a complication of laparotomy is discussed and the factors responsible for its inception and development are presented.

The pathologic process is briefly described. There is extensive parenchymatous degeneration in the various organs with or without an associated infiltration by gas and bacilli.

The clinical picture is one in which an overwhelming toxemia brings death, usually within thirty-six hours after operation. An extraordinary hyperpyrexia occurs associated with hypotension, cold clammy skin and coma. These features should suggest the diagnosis. Crepitation may be present when the abdominal wall is involved. There is evidence of suppression of hepatic and renal function simulating certain types of so-called hepaticorenal insufficiency occurring after operation.

The treatment consists of measures directed at lowering the temperature, combating the toxemia and supporting the circulation. Antitoxin should be administered immediately. The prognosis is extremely grave.

THE BREAST

I. LESION IN RABBITS RESEMBLING CHRONIC CYSTIC MASTITIS

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In the course of detailed studies of the histologic changes in the mammary gland of the rabbit during the growth and sexual cycles certain changes similar to chronic cystic mastitis in man were noted. The entire study will be offered for publication in a special journal. The observations here reported are, however, of sufficient general interest to deserve a wider audience.

Schill [1] in the course of a somewhat similar study incidentally mentioned somewhat similar observations. No pathologic interpretation was made.

During the present studies it was found that in the resting stages (i. e., the male breast, the virgin female breast and the resting postlactation breast) the rabbit's breast presents a histologic picture which is in substance identical with the pathologic picture known in the human breast as chronic cystic mastitis. The elements of this picture are: cyst formation, epithelial hyperplasia and metaplasia, mixed cell infiltration, erosion of the epithelium and scarring of the stroma. One or more of these lesions occurs in more than 90 per cent of resting breasts.

Cyst formation is the most outstanding pathologic feature observed in these studies (figs. 1, 2 and 3). All grades of cyst formation are found, ranging from mild dilatation of the ducts to macroscopic cysts. These are practically always lined by pathologic epithelium. Usually the epithelial lining is metaplastic (figs. 1 and 3). There are also areas of hyperplasia (figs. 1 and 3) in the walls of these cysts. They frequently contain desquamated epithelium. Hyperplasia is manifest by simple increase in the number of epithelial cells (figs. 1 and 2) and by tufting of the duct lining (figs. 3 and 4). Simple hyperplasia is probably the most constant pathologic element present. Metaplasia (figs. 1 and 3) varies in degree from flattening of the epithelium to an extreme attenuation of the cells. Mixed cell infiltration is most noticeable in the stroma underlying the pathologic epithelium (figs. 3 and 4). The

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This article includes a small portion of the work presented in candidacy for the degree of Master of Science, June 1932, University of Virginia.

1. Schill, L.: Recherches sur la glande mammaire, sur les phases qu'elle présente au cours de son évolution et leur déterminisme, Thèse de Lyon, 1912.

cells are of the wandering types. Erosion of the epithelium (fig. 2) is not so frequent as the aforementioned elements. The stroma beneath the eroded epithelium sometimes shows proliferation of connective tissue to the extent of scarring (fig. 2).

These changes occur in the male breast in the young and old alike. The virgin female breast presents a similar picture until estrus, when all these changes are erased and the breast assumes an orderly

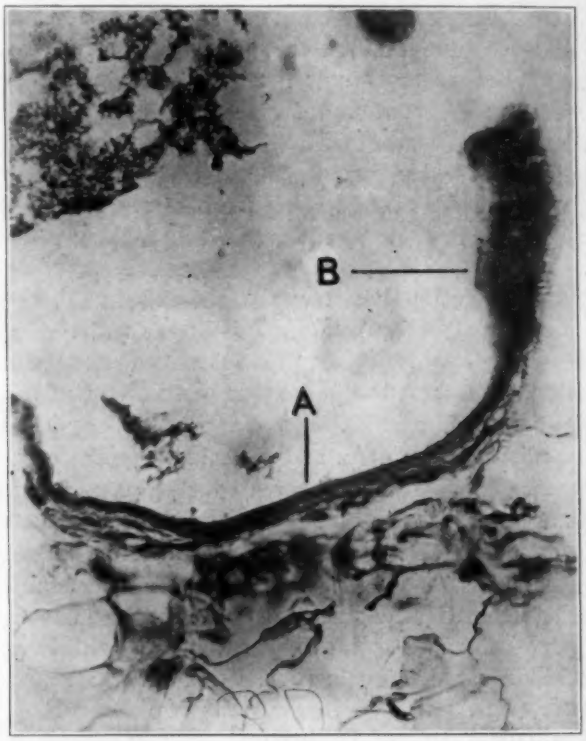

Fig. 1.—Section of male breast showing a part of a large cyst. There is metaplastic epithelium in the wall (*A*) with one area of hyperplasia (*B*). The surrounding stroma is adipose. Hematoxylin and eosin stain; × 335.

morphology. In the multiparous female breast similar pathologic changes are found in the resting postlactation period, but as a rule these changes are not present in any stage of functional activity, i. e., in estrus, pregnancy, pseudopregnancy or lactation. In a few instances slight pathologic changes persist throughout the period of functional activity; in such cases they are never intensified by the hormone stimulation of the breast and they are seen only in the large ducts that are present from the earliest development of the gland. In general, the

more intense the hormone stimulation of the breast, the greater is the regularity of growth and the fewer are the pathologic elements.

The histopathology of chronic cystic mastitis includes just the changes described in the breasts of rabbits, namely, epithelial hyperplasia, formation of cysts, cellular infiltration and proliferation of connective tissue. The present observations are interesting from two points of view. In the first place, to judge by a fairly complete survey of

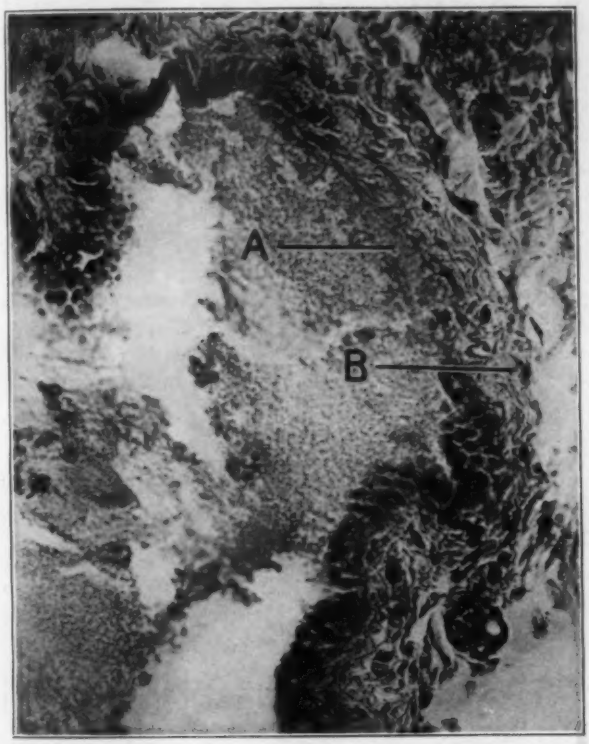

Fig. 2.—Section of male breast showing a part of a cyst with erosion of the epithelium at *A* and with scar tissue beneath. Young fibroblasts (*B*) are seen in the scar. The epithelium on each side of the erosion is hyperplastic. Hematoxylin and eosin stain; × 335.

the literature, with the exception of Schill's observations, no change resembling chronic cystic mastitis has been observed in the rabbit.

In the second place, the relationship between hormone activity and the histologic picture in these breasts is exactly the reverse of the relationship between hormone activity and the clinical picture of chronic cystic mastitis. In the former instance estrus erases the pathologic elements; in the latter instance the premenstrual period of the menstrual cycle intensifies the clinical picture.

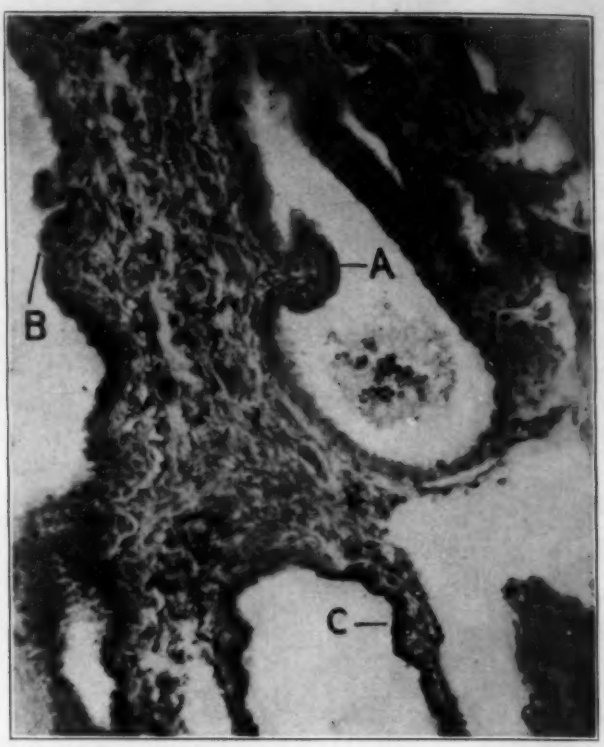

Fig. 3.—Section of male breast showing a part of four cystic ducts. One cyst contains a papillary projection (*A*) and a number of desquamated epithelial cells with a few wandering cells. One cyst shows hyperplasia (*B*) and another shows metaplasia (*C*). There is a mixed cell infiltration in the stroma. Hematoxylin and eosin stain; × 167.5.

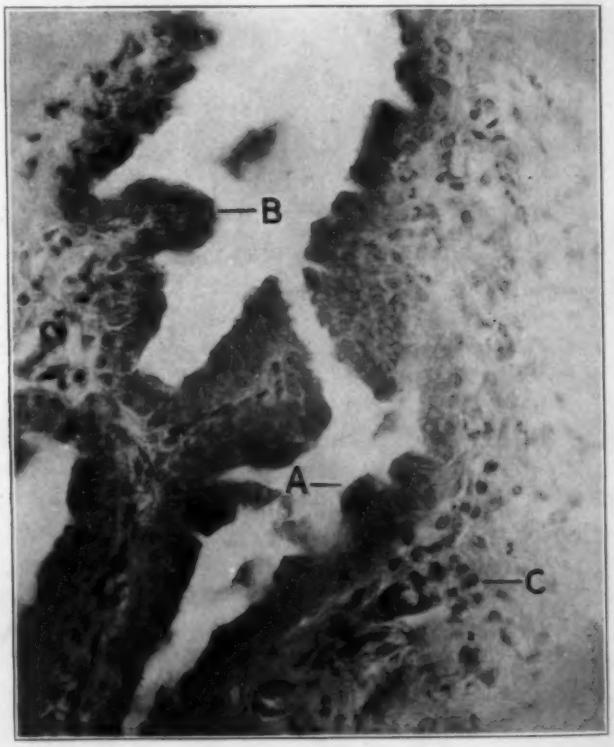

Fig. 4.—Section of male breast showing parts of two ducts with tufting (*A*) and papillary projection (*B*). There is a marked cellular infiltration in the stroma (*C*). Hematoxylin and eosin stain; × 335.

These curious observations do not help to throw light on the etiology of chronic cystic mastitis. They suggest that there is a growth tendency on the part of the epithelial cells which need a hormone for regular orderly development and that when the hormone is absent the cells, subjected to this tendency to develop, do so irregularly. Under this conception the changes in the stroma may be secondary to the epithelial changes.

PRIMARY LIPOSARCOMA OF BONE

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Malignant tumors which arise from preexisting lipoma and exhibit pronounced fatty elements have been described not infrequently since the original articles of Virchow [1] in the middle of the last century. The contributions of Robertson,[2] in 1916, and that of Seids and McGinnis,[3] in 1926, summarize the present knowledge of these tumors. It is noteworthy that these reports are concerned only with those tumors which were found perirenally or in the fascial planes of the extremities.

So far as a reasonable search of the literature will disclose, the only instances of primary liposarcoma of bone seen were the three cases reported by Stewart [4] from the Memorial Hospital, New York, in 1931. Stewart concluded from circumstantial data that his tumors were primary in the bone, and stated "we are not in a position of absolute certainty in stating this." Again, he said: "The only constituent of bone or bone marrow unrepresented in the tumor field seems to be the fat tissue."

There were also a few cases of benign lipoma which were apparently of periosteal origin (Bartlett [5] and Geschickter and Copeland [6]) which in themselves may have been the site of malignant degeneration.

I now present the report of a case which, from the clinical and pathologic study, strongly suggests a periosteal origin of a liposarcoma.

REPORT OF A CASE

History.—L. K. was admitted to the Highland Hospital on Jan. 1, 1932, with the complaint of pain in the left shoulder of four months' duration. The patient was a white, married, American housewife, 30 years of age. During the past fifteen years she had dislocated her left shoulder many times, but aside from a short period of discomfort following this she had had no trouble with the shoulder until four months previous to admission, when she first noted a light aching pain similar to that following dislocation. This had persisted and had

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From the East Orthopedic Service, Highland Hospital; Dr. N. Austin Cary, Chief.

1. Virchow: Virchows Arch. f. path. Anat. **4**:468, 1854; **11**:281, 1857; **32**: 545, 1865.

2. Robertson, H. E.: J. M. Research **35**:131, 1916-1917.

3. Seids and McGinnis: Surg., Gynec. & Obst. **44**:232, 1927.

4. Stewart: Am. J. Path. **7**:87, 1931.

5. Bartlett: Periosteal Lipoma, Arch. Surg. **21**:1015 (Dec.) 1930.

6. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, New York, Am. J. Cancer, 1931, p. 605.

become progressively more severe. She consulted a physician concerning it, who told her that it was "rheumatism" and treated her. During the previous month the pain had become more severe, and coincident with this there began a gradually increasing swelling in the axillary area.

Since the onset there had been a slight fever off and on. She located the pain at the tip of the shoulder. It was made worse by movement, especially anterior flexion and abduction of the arm at the shoulder.

Aside from the aforementioned recurrent dislocations of the shoulder, she had had a heart murmur since the age of 6 and occasional head colds. She had been married 11 years, and had two children, one living and well and the other dead. Her menses were normal, and there was no memory of serious previous illness. The family history revealed no familial or malignant disease.

Physical Examination.—The patient was a poorly nourished, thin white woman lying quietly in bed in no apparent distress. The heart was enlarged to the left with a systolic murmur at the mitral area. The blood pressure was 110 systolic and 55 diastolic; the temperature, 98.4 F.; the pulse rate, 75, and the respiratory rate, 18.

On the upper part of the left extremity was a symmetrical, rounded swelling over the head and trochanter of the humerus. It was not inflamed, and the vessels overlying it were not engorged abnormally. It was cold, smooth and homogeneous on palpation. There was an increase in tension and elasticity suggesting fluid under pressure. The mass lay beneath the deltoid muscle, which was freely movable. The mass was not movable and lacked the feel of an encapsulated tumor. The arm through the proximal end measured 2 inches (5.08 cm.) greater in circumference than the normal right arm. There was only slight tenderness on pressure, but passive forward elevation of the shoulder produced pain.

Laboratory Examination.—The Wassermann reaction of the blood was negative. The blood showed: hemoglobin concentration, 72 per cent; white blood cells, 6,400 per cubic millimeter; polymorphonuclears, 49 per cent; small lymphocytes, 40 per cent, and 11 per cent large lymphocytes. The urine was normal.

Roentgen Examination.—A roentgenogram made on Dec. 31, 1931, of the anteroposterior view of the left shoulder was reported by Dr. C. M. Pearce as showing a rarefaction in the greater tuberosity and upper 2 cm. of the humerus, with a bulging of the cortex over the tuberosity. Neither perforation nor formation of new bone was visible. The marked rarefaction and bulging of the greater tuberosity were suggestive of early formation of bone tumor, but the diffuse mottling in the upper portion of the shaft argued rather for early osteomyelitis.

Examination made on Jan. 6, 1932, in anteroposterior steroscopic views of the shoulder (fig. 1), reported by Dr. W. H. Sargent, showed a destructive process in the greater tuberosity of the humerus, evident in a small rather well defined area about 1 cm. in diameter lying close to the cortex. There was a slight mottling of the bone adjacent to this area, and extending down into the shaft about 2 inches. There was no evidence of rupture through the cortex as yet. In the area of swelling of the soft tissue was a faint shadow lying adjacent to the shaft which suggested periosteal reaction. Conclusions in this case were impossible without the clinical findings. If the patient had had fever and other findings to coordinate it, I should have been inclined to consider the condition as due to infection. Its diffuseness was rather against new growth.

There was no evidence of a pathologic process in the lungs. The cardiac shadow was globular and there was considerable fulness in the auricular area.

Fig. 1.—Anteroposterior roentgenogram of the left shoulder on entry to the hospital. Note the destructive area in the greater tuberosity of the humerus and the mottling of the bone adjacent to this area. In the soft tissues the bulging mass beneath the deltoid muscle can be seen.

Fig. 2.—Photograph of the arm involved with tumor. Note the extreme swelling of the upper part of the arm. The biopsy wound is open, with the tumor extruding.

Course.—A diagnosis was not clear, so further attempts were made to arrive at one. On January 8, an aspiration was done, in the belief that a lesion such as bursitis, osteomyelitis or ganglion could be ruled out this way. This would not be considered good surgical practice, and I feel that in this case it served to stimulate the growth of the tumor. Only a small quantity of bloody material was obtained, which microscopically showed normal blood.

By January 20 (fig. 2) the pain and swelling in the arm had increased considerably, and a specimen of tissue was removed surgically for biopsy. The deltoid muscle was opened by blunt dissection. Immediately on entering the subdeltoid area a large amount of slimy jelly-like material filled the wound. It was grayish-yellow and very friable, with stringiness. A large amount was scraped out from beneath the deltoid muscle, to which it showed no attachment. There was no capsule. The only point of attachment was to the tuberosity of the humerus. The bone at this point was definitely infiltrated with the tumor, and was easily perforated with a blunt hemostat. The involvement of bone extended down the neck from 2 to 3 cm. The tumor had a free blood supply which necessitated packing to control hemorrhage at frequent intervals. Specimens of the bone and tumor tissue were removed and examined by Dr. G. Moore, who reported as follows: The most striking characteristics from a microscopic standpoint were the remarkable variations in the size and shape of the cells and the number of bizarre nuclear forms. Individual cells varied from small round or spindle cells to enormous giant cells of both mononuclear and multinuclear forms. In the larger cells the outlines were indistinct, and there was a curious multiplicity of pattern. The cytoplasm showed many vacuoles which, on frozen section, stained with sudan III, were found to contain fat droplets. The nuclei were likewise peculiarly diversified, and showed a moderate number of mitotic figures. Tumor cells dominated the picture, with little evidence of supporting fibrous tissue. The blood supply was free, and there were many hemorrhagic areas. The picture was that of a malignant mesoblastic tumor, which, because of its lipoid content, might well be placed in the group of the liposarcomas.

With a proved diagnosis, roentgen therapy was instituted by Dr. W. H. Sargent, it being known that many reported liposarcomas are radiosensitive. Numerous transfusions of citrated blood were also undertaken. When a checkup roentgenogram of the chest failed to show any metatases, a radical shoulder girdle amputation was decided on. This was done on February 23. The patient withstood the surgical procedure satisfactorily, but died six hours later of delayed shock.

Autopsy.—A complete autopsy was performed by Dr. George Calvin, who reported as follows: The general external examination revealed a normal condition except for the absence of the left arm at the shoulder girdle, apparently amputated recently. The right lung showed heavy adhesive pleuritis throughout the entire lower lobe. There was no free fluid. The cut sections were normal except for scattered small, soft, metastatic nodules. Sections of the nodules in the lung showed them to be composed in large part of the same cells containing lipoid found in the primary tumor of the arm. The heart showed adhesive pericarditis, and the mitral valve sclerosis and retractions. The liver, spleen and kidneys revealed no metastases and except for congestive change were normal.

The amputated arm was examined immediately postoperatively, and frozen sections were stained with fat stains. These showed the previously reported pathologic process, but served to demonstrate the marked preponderance of fatty elements in the tumor.

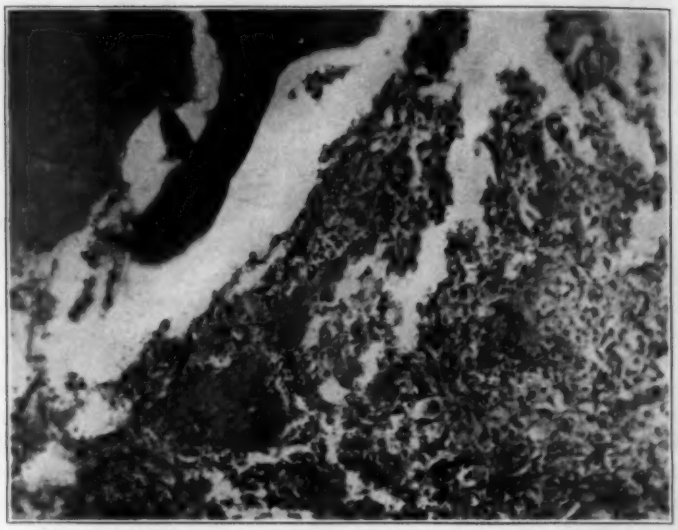

Fig. 3.—Photomicrograph of the tumor showing the involvement of bone. The vacuolated areas, when freshly stained with sudan III, were shown to be filled with fat; × 200.

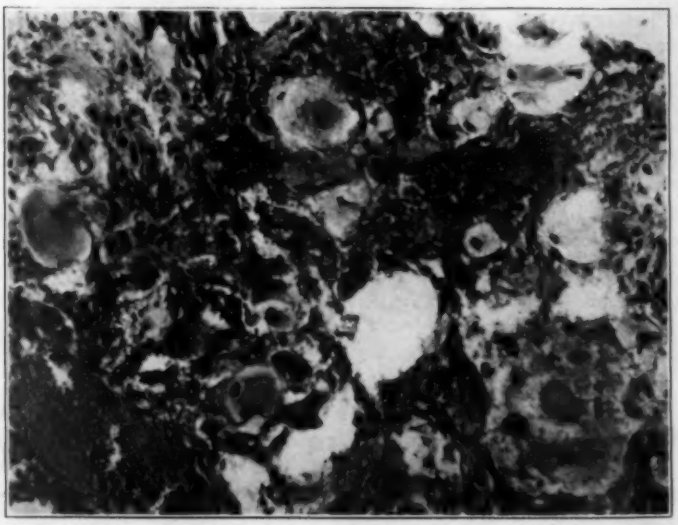

Fig. 4.—Photomicrograph of section of the tumor tissue showing various-sized cells and diversified nuclei; × 500.

COMMENT

It is well known that fatty tumors termed "lipoma" may undergo sarcomatous change, and the first impression was that this was such a tumor. There were, however, several factors which did not coincide with this point of view. First, the tumors that have been reported, few of which involved the upper extremity, did not involve the bone, but arose in the fascial planes from a preexisting lipoma which was always encapsulated, and the history of its presence preceded for long periods its malignant change. Only one instance of involvement of bone was noted by Stewart, that of Neinhuis, in which case the process was considered metastatic.

The clinical picture in this case was more characteristic of so-called periosteal sarcomas, but the pathologic findings did not fit this classification. That this was not a benign periosteal lipoma which had undergone sarcomatous change would seem evident from the lack of encapsulation and the absence of tumor prior to the onset of severe symptoms.

The osseous involvement was apparent in the earliest roentgenogram, and at the time of biopsy there was no infiltration of the subdeltoid sheath, which would have been a much more logical site for local metastases or invasion than the cortical bone if the tumor had arisen extraperiosteally.

The histologic picture of the tumor both locally and in the myriad of small metastases in the lungs, which were not demonstrable by x-ray film, strongly suggests that this was a tumor of fatty origin. The influence of the trauma from repeated dislocations of the shoulder is of definite interest and must be assumed to have been a factor in the origin or spread of this new growth. It may be well in the future to stain more of the frozen sections of biopsy specimens with some standard fat stain to establish more accurately the frequency of these malignant processes.

SUMMARY

The general subject of malignant fatty tumors involving bone is considered, and a case reported which, from the clinical and pathologic evidence, strongly suggests its origin from the fatty elements of bone. It is hoped that more frequent use of fat stains at biopsy will disclose more facts in this obscure tumor field.

CHANGES IN THE BONES OF EXTREMITIES AMPUTATED BECAUSE OF ARTERIOVASCULAR DISEASE

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AND
MAURICE M. POMERANZ, M.D.
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Histopathologic descriptions of bones of extremities amputated because of gangrene, contingent on vascular occlusion, are practically nonexistent. In caring for patients in whom gangrene of the extremities is developing, it is often the practice, in the course of clinical observation, to make roentgenographic records of the diseased parts. The records are generally taken with a view to ascertaining the extent, severity and character of the changes in the soft tissues and, more particularly, of those in the bones. But the sparsity of pathologic studies of bones of gangrenous extremities necessarily limits the intelligent roentgenographic interpretation of any changes that may exist.

The presence of extensive roentgenographic changes in all of the bones of the right lower extremity of a patient for whom a diagnosis of thrombus in the right common iliac artery, probably extending into the aorta, was made, gave stimulus to our study (fig. 1). By this work we hoped to clarify the subject of histopathologic changes occurring in the bones of surgically amputated extremities with vascular occlusion and resultant partial gangrene. One of our special objects was to coordinate particular histologic changes with corresponding roentgenographic abnormalities, thus providing a factual basis for roentgenographic interpretation. Eight specimens were studied; in most instances an opportunity was afforded for the gross and histologic investigation of the femur, tibia and the tarsal, metatarsal and phalangeal bones. We were particularly interested in ascertaining the condition of the bones high above the level of gangrene and infection. In evaluating the gross, roentgenographic and histologic changes, the necessity of due regard for the rôle played by infection, inactivity and the so-called trophoneurotic influences was borne in mind.

Mueller [1] seems to be the only person who has previously undertaken an inquiry of this nature; he examined the bones from four lower extremities, amputated because gangrene of as many as from two to three toes had proceeded from arteriosclerosis and vascular occlusion

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1. Mueller, W.: Beitr. z. klin. Chir. **138**:614, 1926.

(the nongangrenous portion of the extremities likewise showed evidences of circulatory failure). In the interstitial lamellae of the cortical bone at some distance above the site of general tissue necrosis (even as high as in the tibia), he found and stressed the prominence of widespread empty bone cell lacunae. The bone cells of the haversian lamellae as well as those of the ground lamellae (especially the inner lamellae) and the spongy trabeculae stained well and were not degenerated. Mueller considered necrosis or death of the bone cells of the cortical interstitial lamellae (or others at a distance from the haversian canals) to be the direct effect of disturbance and diminution of the circulation and concluded that this demonstrated a differential reaction of the bone cells to partially diminished circulation, the cells of the interstitial lamellae of compact bone being particularly sensitive in that respect. The unfavorable anatomic position of the cells was considered responsible for their greater susceptibility. Furthermore, Mueller reported that the myeloid and connective tissue elements of the marrow were in all four instances well preserved, and that they showed no evidences of osteogenic activity, nor were regenerative phenomena apparent to any degree in the bones.

For the purpose of control, Mueller examined a number of corresponding bones from older persons without gangrene, who ranged in age from 70 to 89 years. In these subjects absence of nuclear staining of the interstitial lamellae of compact bone could also be observed, but it was never of such regularity or extent as that which developed in the arteriosclerotic patients with gangrene; the degree was on the whole proportional to the age. Likewise, no regenerative phenomena were found in the bone or the marrow of these specimens. In the control, nongangrenous extremities, extensive changes in the bone, he believed, could be related to the existence of arteriosclerosis.

INTERSTITIAL LAMELLAE IN THE COMPACTA OF OUR CONTROLS

There is no doubt that Mueller was correct in emphasizing that the cells of the cortical interstitial lamellae in his amputated specimens had a greater susceptibility and tendency to die. This predisposition exists even in normal bone, despite the lack of attention focused on it by histologists generally. The nature, the mode of formation and the position of the interstitial lamellae of normal compact bone bespeak the unmistakable inherent disposition favoring such susceptibility. Our own histologic studies of bone have indubitably indicated this predilection: Interstitial lamellae are fragments of old and splintered haversian systems; in the disintegration of these systems, interstitial lamellae form an important supporting mass for newer haversian systems and as a result become disadvantageously placed for the receipt of nutrition. This is not the fate of the cells of the interstitial lamellae of compact

bone alone; wherever bone cells are disadvantageously situated for the reception of nutrition, they tend to die. A simple example of this tendency is the condition of the deeply placed cells in a compact and sclerosing calvarium; here the deeply embedded cells between obliterated or obliterating diploe evidence the greatest absence of staining. A slight degree of degeneration and death of the cells of deeply placed lamellae of compact bone are normal manifestations even in young adults; with increasing age the degree and extent become progressive, provided the bone always remains compact. This gives no abnormal appearance roentgenographically.

The foregoing assertions are based on a study of numerous sections of bone observed in the course of routine examinations and specifically on the character of the changes seen in the femurs of six patients (ranging from 8 to 62 years of age) who died from various causes and whose extremities were not gangrenous. Cross-sections were taken through the middle of the femurs.[2]

Case 1.—One of the six patients, a woman, aged 36, died of cardiac failure, associated with rheumatic endocarditis and terminal pulmonary infarction. The cross-section of the femur showed normal general architecture, the haversian canals being of the usual diameter. On the whole, the cells and the ground substance of the haversian systems stained well. An occasional haversian system with a plugged central vessel was observed, and naturally the nuclei and the ground substance of an osteon of this sort stained poorly. The interstitial lamellae throughout the section stained more poorly than the rest of the lamellae. In some of this interstitial bone all of the nuclei were absent from their lacunae; in other portions only a few poorly staining cells were to be seen, and in still other areas as many as half of the cells were in evidence. The inner and outer ground lamellae were for the most part as well preserved as the haversian lamellae, while the cells of the spongy trabeculae stained well; the marrow also showed nothing abnormal.

The foregoing description applied generally to several of the sections of the other femurs studied (fig. 2). There were variations dependent

2. In studies of this nature, the utmost attention to technical details in the methods of preparing the sections is imperative. Otherwise, the appearance of artefacts, particularly in sections of compact bone, invalidates the usefulness of the examination. First, in preparing compact bone for histologic study, it is necessary to take thin segments from 2 to 3 mm. in thickness for fixation; next, these segments should be fixed promptly after removal from the body. For the best preservation of the cellular elements, we prefer a fixative containing bichromate (Helly's fluid); decalcification with 5 per cent nitric acid is then satisfactory; embedding must be in pyroxylin (celloidin) or the sections will be fragmented; careful staining with hematoxylin to the point of overstaining and proper decolorization and differentiation are also necessary. Emphasis on these details may seem elementary, but it is vitally important to observe these rules in obtaining reliable as well as good histologic sections. For further details, the reader is referred to other publications (Jaffe, H. L.: Methods of Histologic Study of Normal and Diseased Bone, Arch. Path. **8**:817 [Nov.] 1929. Riemer, B.: J. Techn. Methods **13**:72 [March] 1934).

Fig. 1.—A roentgenogram demonstrating the character of the lesions in some of the bones of the foot. General porosity is apparent; small, punctate areas of rarefaction are clearly seen; these are pronounced in the compacta of the metatarsal bones.

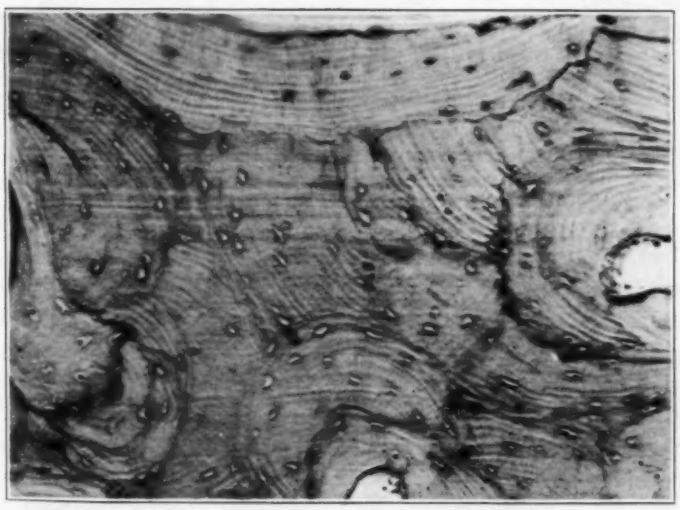

Fig. 2.—A small area from a femoral cortex, in cross-section. The patient was 36 years of age. Nuclei are absent from the interstitially placed bone; the nuclei of the osteons stained well; × 300.

on the age of the patient, the nature of the illness, the character of the terminating disease and other features. Even in the femur of the 8 year old subject, the cortical interstitial lamellae showed a leaning in the same direction.

CASE 2.—In another patient, a woman, aged 44, who had progressively lost weight for about a year and who died of atrophic cirrhosis of the liver and its usual concomitants, the femoral section disclosed the presence of a moderate degree of simple osteoporosis. This was not sufficient to reduce the interstitially placed bone materially; therefore it showed fairly large areas with absence of nuclear staining.

CASE 3.—The femoral section of one patient who died shortly after admission to the hospital of infarction of the cardiac muscles due to coronary occlusion also presented a slight degree of osteoporosis. The patient had suffered from diabetes mellitus of moderate severity and showed at postmortem examination, in addition to other changes, extensive generalized arteriosclerosis; the femoral artery in the vicinity of the region from which the piece of femur had been removed evidenced definite thickening with medial sclerosis and early calcification. As in the other sections of bone, the cells of the interstitial lamellae stained most poorly, but, curiously enough, the changes were less advanced than those in the other cases; that death occurred rather quickly may account for this.

What conditions the greater susceptibility of the cells of the interstitial lamellae is unknown; whether its prevalence depends directly on the advent of arteriosclerosis in the extra-osseous blood vessels is a moot question. Whether disintegration and death of the cells of deeply placed lamellae of compact bone precede the inception of such changes as are produced by senile osteoporosis or whether they contribute to the induction of brittleness so often found in senile bones is still open to investigation.

BONES OF EXTREMITIES IN WHICH CHRONIC VASCULAR DISEASE LONG PRECEDED GANGRENE

In this laboratory during the past few years there has been a striking reduction in the number of extremities received that were amputated because of gangrene. This is only a reflection of the great improvement in the clinical care of patients with impending gangrene. Previously, its first appearance in the toe of a diabetic patient was usually the signal for high amputation to eliminate any possibility of progressive infection and diabetic coma; now, on the contrary, conservative measures often result in recession of the serious local changes. Often, too, patients with considerable organic vascular disease of the extremities may entirely escape amputation, although they have been in imminent danger of extensive gangrene. When such a patient finally has to undergo amputation, it is usually because the infection cannot be controlled, although treatment may have delayed the necessity for amputation for months. Thus, the long interval of time allows such factors as infec-

tion, inactivity and the so-called trophoneurotic influences, in addition to the circulatory disturbance, to assert themselves. In fact, the strong and natural tendency toward the development of collateral circulation frequently reduces to a place of second importance the effect which the vascular obstruction has on the changes in the bones.

These premises are borne out by the results of examination of the right lower extremity in the following case:

CASE 4.—A man, aged 68, had had his left lower extremity amputated four years previously because of gangrene of the toes. Difficulty with the right lower extremity began about two years before his last admission. At that time the right foot suddenly became cold and insensitive; he suffered from cramps in the foot and could not walk. Examination then revealed areas of anesthesia over the dorsal surface of the foot; a bluish discoloration at the tip of the large toe, in the vicinity of the toe-nail, appeared; finally this area was converted into a gangrenous bleb. With conservative treatment the patient's condition slowly improved, the local symptoms receding, so that he was able to leave the hospital. About a year later gangrene appeared in the toes, progressing slowly; during this time parts of the foot sloughed off. Finally a fulminating infection necessitated readmission for amputation. For almost a year and a half the patient had been confined to bed.

The amputated specimen demonstrated considerable infection and sloughing of the foot; some parts of the tarsal bones were visible through the slough; the infection and ulceration extended a distance up the leg. When the soft tissues of the leg and ankle were dissected, necrotic muscles, tendons and fascial tissues were everywhere encountered. The popliteal artery was extremely atheromatous and calcified, as were the anterior and posterior tibial arteries.

All of the bones were greatly affected even grossly; the femoral cortex was thinned as a result of a pronounced eccentric atrophy that had considerably enlarged the marrow cavity; anteriorly the cortical reduction had proceeded to such an advanced degree as to leave a mere shell, plainly eroded on the inner surface; the vascular canals of the femoral cortex were visibly enlarged; the medullary cavity contained soft, almost liquid, fatty marrow and delicate bony trabeculae (fig. 3). The tibia also cut with great ease; the upper portion of the medullary cavity was likewise filled with soft, fatty marrow, while in the lower third the marrow contained a number of liquefaction cysts. There was edema of the periosteum, and subperiosteal osteophytic new formations were observed in its upper portion. The tibial cortex, although not greatly thinned, was much more porous than normal.

Both the astragalus and the calcaneus were atrophic to such a degree that they could be compressed between the fingers; they were the only tarsal bones which were complete and which retained their original shape and position. Within the astragalus there was a large triangular, wedge-shaped, whitish-yellow focus of bone which was definitely demarcated from the surrounding bone; this extended to beneath the articular cartilage and occupied a large area in its posterior extremity. There was a similar but smaller triangular focus of necrotic bone at the anterior extremity of the astragalus. Otherwise, this bone and the calcaneus showed extensive resorption of the spongy trabeculae; large portions were occupied by soft, fatty marrow. Grossly, these bones did not present evidence of osteomyelitis, although the surrounding soft tissues were extremely necrotic and partly hemorrhagic (fig. 4 *A* and *B*).

Fig. 3.—Roentgenogram of the sagittally sectioned femur. Extensive cortical thinning and rarefaction are evident, as also the enlargement of the medullary canal. For the histologic appearance see figure 5.

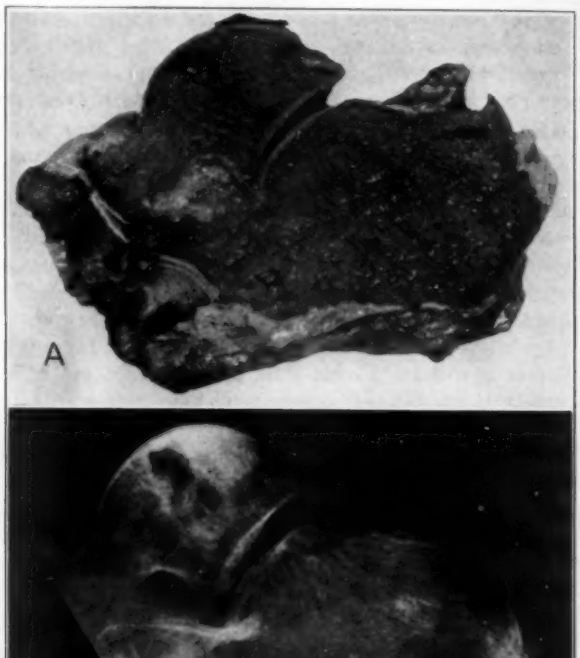

Fig. 4.—*A*, a triangular, wedge-shaped focus of necrotic bone in the posterior portion of the astragalus. The pronounced rarefaction of the rest of the astragalus and calcaneus is evident in this photograph, which is slightly reduced from normal size. *B*, roentgenographic appearance of the same necrotic focus in the astragalus, which casts a dense shadow (fig. 6).

Histologic study of the bones again pointed to the secondary importance of vascular disturbance; the changes in the bones were clearly much more dependent on the effects of infection and inactivity. A number of femoral cross-sections confirmed the gross appearance of rarefaction from the medullary side; the spongified cortex contained congested and vascular myeloid marrow in its enlarged spaces. On the other hand, there was little cortical resorption from the periosteal side. Furthermore, the sections revealed that many of the haversian canals, particularly near the periosteal surface of the cortex, contained pink-staining plugs; the nuclei within such osteons showed partial or complete absence of staining. In addition, some of the nuclei of other haversian systems also demonstrated poor staining; in places the nuclei were entirely absent from their lacunae. The interstitially placed bone, however, most pronouncedly illustrated the absence of nuclei from their lacunae, but this bone was relatively slight in amount (fig. 5). A longitudinal section through one of the femoral condyles disclosed rather good staining of the nuclei of the spongy trabeculae and of the intertrabecular fat. Cross and longitudinal microscopic sections from the tibia showed, aside from the rarefaction due to eccentric atrophy, absence of nuclear staining from the interstitial bone as the principal feature.

The microscopic examination of the astragalus demonstrated the posterior, triangular, wedge-shaped, infarct-like area to be composed of thick, spongy trabeculae of dead bone; the marrow between the trabeculae had not been vascularized; this infarcted area was surrounded by vascular, fatty marrow, but none of its vessels had penetrated the necrotic marrow within the infarct area. The articular cartilage overlying the infarcted area was also necrotic (fig. 6). The portion of the astragalus that had become atrophic through disappearance of the trabeculae contained somewhat vascular and edematous fatty marrow; within this marrow a number of newly formed osseous trabeculae were to be seen, as well as a moderate amount of newly proliferated fibroblastic tissue. At the base of the bone, a large area of subchondral infection was to be found; no evidence of thrombosis of the nutrient vessels was discovered. The spongy trabeculae of the calcaneus were pronouncedly atrophic; the intertrabecular fatty marrow was edematous and showed engorged blood vessels. The nuclei of the atrophic trabeculae stained well. The fat and soft tissues about the bone were infected; the infection which extended along the achilles tendon invaded the bone and produced local areas of osteomyelitis. Thus in the astragalus and calcaneus much of the atrophy apparently was due to infection and inactivity, while the infarct-like lesions were to be attributed to occlusion of the vessels supplying these areas.

That arterial disease of long standing may exist when the bones do not show significant roentgenographic changes was brought out by a number of our specimens, one of which is described in the succeeding paragraphs.

CASE 5.—A woman, aged 59, was first admitted on Oct. 17, 1932, with a history of pain in the left large toe, of two weeks' duration. The pain was chiefly nocturnal. No dorsal pedis artery was palpated. After medical therapy had been carried out for two months, the patient was discharged. On Feb. 1, 1933, she was readmitted because of the sudden appearance of gangrene of the left large toe and an ascending inflammation of the proximal part of the foot. A blood culture on admission gave positive results. The patient died in spite of amputation of the leg.

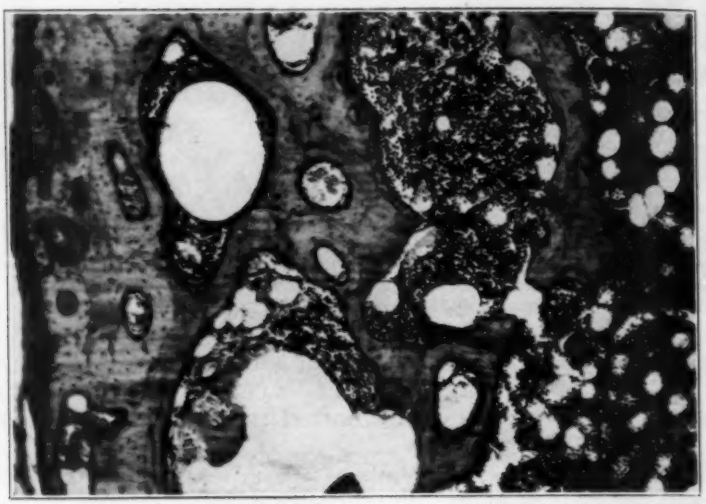

Fig. 5.—An extremely rarefied and spongified femoral cortex; the enlarged spaces are filled with myeloid marrow; the resorption from the periosteal side is insignificant. The pronounced enlargement of vascular canals resulting in the formation of large spaces has reduced the cortical thickness to the degree observed in figure 3. The interstitially placed bone is relatively slight in amount; × 30.

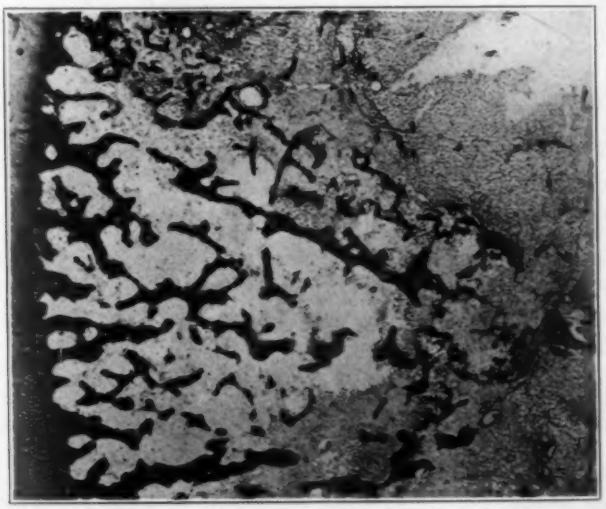

Fig. 6.—The thick but necrotic trabeculae of the triangular, wedge-shaped focus in the astragalus demonstrated by figure 4; × 5.

The specimen showed the large toe discolored a reddish, purplish black as far as the metatarsal phalangeal joint; the second, third and fourth toes were also discolored, from reddish purple to black, especially on their ventral surfaces; the small toe showed no evidence of gangrene. Frank purulent infection was absent from the gangrenous toes; there was no perforating wound anywhere. The muscles of the leg were found to be reddish and fairly well preserved; when the incision was carried to the foot the tissues in the nongangrenous area showed nothing in particular except edema; in the gangrenous regions, the tissues were hemorrhagic and edematous. The anterior tibial, posterior tibial and dorsalis pedis arteries were

Fig. 7.—The roentgenogram of the foot of a woman, aged 59, in whom gangrene was impending for some months; amputation was performed because of gangrene of several toes, which appeared suddenly. Nothing striking is seen except the rarefaction of the terminal phalanx of the large toe. Compare this with figure 1.

found to be occluded by a thrombus. Roentgenograms of the specimen were taken, but none of the bones of the foot or leg showed anything striking in the film, although the terminal portions of the four toes were definitely gangrenous; at most there was only the slightest indication of atrophy of all of the bones. This, considering the age and previous disability, is comprehensible (fig. 7).

Microscopic sections of the tibia showed that most of the cortical interstitial lamellae stained poorly; some of its cells still stained fairly well; most of the

cells about the haversian lamellae stained well. Numerous sections from the other bones, furthermore, demonstrated that the more closely situated they were to the sites of impaired circulation, the greater was the nonstaining of the bone cells; always it was the deeply situated cells that were degenerated (fig. 8). The large toe, which showed massive gangrene of the soft tissues, demonstrated the greatest degree of devitalization of its bones.

Four other specimens from patients suffering from arteriosclerotic gangrene of a lower extremity, with or without attendant diabetes mellitus, resembled the two specimens detailed earlier. All six specimens illustrated again what has been repeatedly stressed: No matter how advanced the organic vascular disease may be, no matter how long since the inception of the vascular disturbance, no specific or characteristic

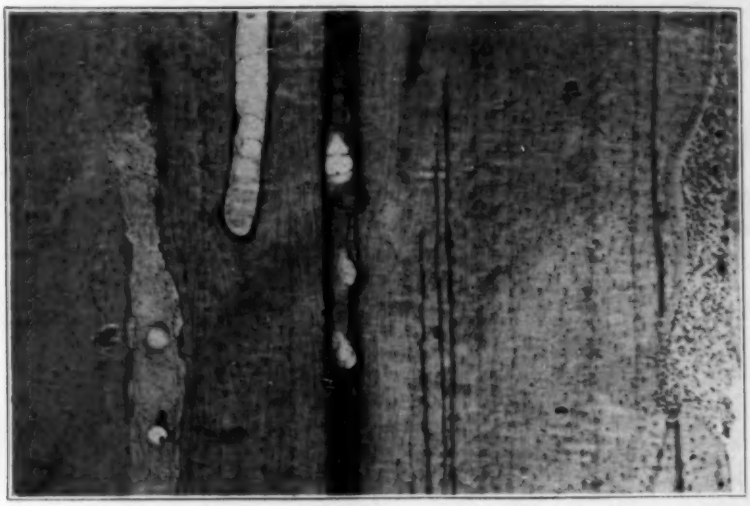

Fig. 8.—The cortex of the proximal phalanx of the second toe of the foot is shown in figure 7. Grossly, the bone was apparently normal. The soft tissues about the bone were not gangrenous. Microscopically, the cortex showed extensive areas of absence of nuclear staining. Roentgenographically this phalanx showed nothing unusual; × 150.

changes in the bones are consistently demonstrable roentgenographically (this is in marked contrast to the well known changes produced in the terminal phalanges and evidenced roentgenographically by Raynaud's disease and scleroderma). This roentgenographic and histologic correlation demonstrated, furthermore, that unless the histologic processes were clearly understood, a strong possibility for misinterpretation of the roentgenograms exists. For instance, the bones of a gangrenous toe may appear roentgenographically normal, while histologically its phalanges may show an extensive, purulent infection of the medullary cavities; osteomyelitis, therefore, exists, but the roentgenologist is at

a loss to recognize it, as no periostitis is present. The periosteal reaction is naturally absent because of the devitalization of the soft tissues about the bone. Again, the roentgenographic appearance of a phalanx or a metatarsal bone may be within normal limits, or the roentgenographic shadows of such bone be even sharper than those of the adjoining ones; by contrast, the contiguous bones appear atrophic, but histologically these more clearly defined bones are likely to be completely necrotic.

Fig. 9.—Demonstrating part of the femur, tibia and fibula of a patient in whom an acute occlusion of the common iliac artery was followed a few months later by marked rarefaction of all of the bones of the extremity. Collateral circulation was adequate to prevent immediate gangrene, although it was not sufficient for normal nutrition. Figure 1 shows the roentgenographic changes in the bones of the foot of this patient. Figure 11 shows the character of the microscopic changes in the femur.

They are sharply outlined in comparison with their neighbors because they have undergone rapid necrosis, while the neighboring bones may still be viable, thereby allowing atrophy to supervene.

If a bone or part of a bone becomes rapidly devitalized and if circulatory adjustments are made so that blood is resupplied to the bone,

after a little time an active revascularization occurs; the portions of the bone which have not undergone a revivescence become resorbed and replaced by new bone. In this event, the later roentgenographic appearance will be that of a spotted, punctate rarefaction (figs. 1 and 9). These punctate shadows of increased permeability are the result of enlargement of previously existent vessel canals and cortical erosion, particularly from the periosteal side. In regard to the latter feature,

Fig. 10.—Roentgenogram of part of the foot of a man, aged 43, who suffered from thrombo-angiitis obliterans. On admission the foot was swollen, but the leg on that side was atrophic; the dorsalis pedis artery and the posterior tibial artery were not palpable; an indolent ulcer was present on the dorsal surface of the second toe. Note the rarefaction of the bones. The roentgenographic appearance is suggestive of Sudeck's "acute atrophy." Compare this roentgenogram with figure 1. The rarefaction shown in figure 1 was due to the resorption and erosion of necrotic bone.

diabetic patients with arteriosclerosis and gangrene are so predisposed to extensive infection that if amputation is delayed for a considerable time, the badly devitalized bone, because of infection, is a potential infected sequestrum and therefore is not regenerated. In arteriosclerotic

patients, therefore, some degree of chronic atrophy is likely to be encountered roentgenographically in the absence of frank clinical gangrene and infection, which complicate the picture.

No cases of thrombo-angiitis obliterans are included in this histologic study, as none were available for examination. This further attests to the value of the conservative medical treatment that has been given these patients within the last few years. We have, however, seen roentgenograms of the feet of many such patients with impending gangrene or with marked circulatory disturbance without gangrene; these bones are prone to show the spotted, punctate appearance (fig. 10). Since we have not had bones of this sort under histologic observation, we cannot say with certainty what conditions such roentgenographic manifestations; it seems fair, however, to infer that the spotted appearance is the result of substitution of new bone for devitalized bone by the process of creeping replacement, and that the shadows which are due to increased permeability are the result of cortical erosion and enlargement of spaces in the vessel canal.

BONES OF EXTREMITIES AFFECTED BY ACUTE VASCULAR OCCLUSION

It is well known that obstruction of an otherwise normal artery supplying an extremity need not lead to necrosis and gangrene of the part. If circulatory interference has been severe, the histopathologic changes in the bones will depend on the completeness of the circulatory interruption, the length of time that elapsed between the onset of the gangrene and the amputation and the degree of circulatory restoration that had been spontaneously inaugurated. Thus, when there is prompt amputation, the histopathologic examinations may in certain instances disclose extensive or little necrosis of the bone, but in any event the roentgenographic studies will demonstrate that such bone casts rather normal shadows. On the other hand, if injury to the tissue has been severe but considerable circulatory restoration has delayed the amputation for a long time, both roentgenographic and histopathologic changes are observed.

The approach by experimental study to more definitive information as to the effects of acute vascular occlusion on the soft tissues and bones of the extremities has not been productive of much enlightenment. It has proved extremely difficult to produce gangrene in an extremity of an experimental animal through vascular occlusion; to do so, one must eliminate the possibility of the development of a sustaining collateral circulation; in normal animals, the absence of serious functional impairment at the time of ligating the vessels makes the prognosis good as regards viability of the part. The following experimental examples attest to the great difficulty of producing changes in the bone in the

adult animal or of influencing the growth of the bones of a younger animal. Latarjet [3] ligated the femoral artery in young rabbits, while in still younger rabbits he ligated the femoral artery and destroyed the nutrient vessel of the tibia; in spite of these procedures, he observed no disturbances in the growth of the bones in any of his animals; the obturator arteries became the main source of arterial supply to the extremities on which operation had been performed. Grey and Carr,[4] working with dogs and rabbits (of no stated age), concluded that venous congestion through occlusion of a large vein led to no recognizable changes in the bone structure of the parts on which operation had been performed; while local anemia due to arterial ligation likewise occasioned no atrophies of the bone as long as the part remained functionally active; these conclusions were based solely on roentgenographic studies. In ligating in rabbits the external iliac artery or vein or both simultaneously, Benassi [5] found no changes in the growth or in the histologic and roentgenographic appearances of the bones; some of the animals were adults and others about 1 month of age at the time of operation.

However, Brooks and Martin [6] induced gangrene in the lower extremities of about 72 per cent of their rabbits when the common iliac and external iliac arteries were ligated proximal and distal to the origin of the hypogastric artery. In a second series in which there was added to this procedure ligation of the common iliac vein, the incidence of gangrene was only about 33 per cent. Holman and Edwards [7] also observed that when the common iliac artery and inferior vena cava were simultaneously ligated in eighteen rabbits, gangrene developed twice, while in ten rabbits in which the common iliac and external iliac arteries and the inferior vena cava were simultaneously obstructed gangrene did not occur.

Only when an experimental vascular obstruction is severe enough to produce gangrene of the soft parts are changes in the bone also clearly manifest; at such times, necrosis of the bone results. With frank, irreparable gangrene of a part, all of the tissues die and consequently nothing special can be said concerning the distinctive behavior of such bones under experimental conditions. Burckhardt's [8] experiments shed little additional light on this subject; he wound an elastic band as tightly

3. Latarjet, A.: Compt. rend. d. l'Assoc. d. anat., supp., 1912, p. 72.

4. Grey, E. G., and Carr, G. L.: Bull. Johns Hopkins Hosp. **26**:381, 1915.

5. Benassi, E.: Arch. ital. di chir. **28**:49, 1931.

6. Brooks, B., and Martin, K. A.: Simultaneous Ligation of Vein and Artery, J. A. M. A. **80**:1678 (June 9) 1923.

7. Holman, E., and Edwards, M. E.: New Principle in Surgery of Large Vessels; Ligation of Vein Proximal to Site of Ligation of Artery; Experimental Study, J. A. M. A. **88**:909 (March 19) 1927.

8. Burckhardt, H.: Beitr. z. klin. Chir. **138**:625, 1926-1927.

as possible around the forelegs above the wrists of rabbits from 3 to 4 months old, the elastic being permitted to remain for various lengths of time up to more than twelve hours; after twelve hours, complete necrosis of the part occurred; many of the animals bandaged for less than twelve hours showed paralysis, ulceration and complete loss of hair in the affected part; the damage to the part was on the whole proportional to the length of time the elastic was applied. On the basis of histologic examinations, Burckhardt believed that he could demonstrate by these experiments a greater sensitiveness of the bone to vascular injury, as the necrosis of the bone was observed long after all traces of the injury to the soft parts had disappeared. In the regeneration of bone, the necrotic portions underwent creeping replacement (it is interesting that Burckhardt made no particular mention of lacunar resorption); most of the regeneration was from the marrow side, with formation of endosteal bone. It is worthy of comment, in connection with the theme of this paper, that Burckhardt found roentgenologic study of the extremities of no value in drawing conclusions concerning conditions of the bone during regeneration. Therefore, all that can be gleaned from these experiments is that when bone and marrow are seriously but not irreparably injured by circulatory obstruction, regeneration of bone proceeds surely but more slowly (as is natural) than regeneration of the soft parts.

The bones of the right lower extremity of a colored man, aged 45, demonstrated the extent to which changes of the bone may proceed after acute vascular occlusion.

Case 6.—While walking the patient suddenly experienced pain in the right lower extremity, which began on the inner aspect of the sole and radiated as high as the middle of the thigh. The sudden attack of pain was immediately followed by a feeling of numbness from the knee down. As the patient expressed it, the extremity "felt dead," and it was unable to bear weight. Five months later he was admitted to the hospital, when the right lower extremity was atrophic; femoral arterial pulsation was not palpable; the blood pressure in the involved extremity was 0 systolic and 0 diastolic, while in the left lower extremity it was 180 systolic and 96 diastolic; there were paresthesia and coldness of the diseased limb but no gangrene; the Wassermann test of the blood was negative. All of the indications (including a roentgenogram of the pelvis which showed a shadow in the region of the right common iliac artery) pointed to the existence of a thrombus in the common iliac region, possibly at the bifurcation of the aorta, the clot straddling this region. Collateral circulation was adequate to prevent gangrene, though not sufficient for normal nutrition, for pain in the extremity was becoming progressively worse.

Roentgenograms of the bones of the extremity revealed extensive changes; disseminated throughout were areas of rarefaction involving both cortical and spongy bone; these presented themselves as round or somewhat elongated shadows, the result of increased permeability to radiation. In addition, the bones everywhere cast a less dense shadow than normal. The anterior portion of the femoral cortex was particularly rarefied (figs. 1 and 9).

The existence of a generalized lymphadenopathy prompted the removal of a gland from the right inguinal region; the day following, a burning sensation developed in the right foot; four days later, trophic disturbances over the foot were more marked; within ten days, ulceration of the skin at the base of the great toe appeared; within three weeks definite dry gangrene of the large toe and of the third and fourth toes with superficial ulceration was manifest; five weeks after this, biopsy and an amputation at the midthigh were performed.

Dissection of the specimen, which consisted of the right foot and leg and the lower 8 inches (20.32 cm.) of the femur, disclosed an extremely marked atrophy of the soft tissues. The large toe was gangrenous to the metatarsal phalangeal joint, and this was the condition in regard to the other toes. Dissection of the anterior and posterior tibial arteries showed that neither they nor the branches were occluded; the lumen of the popliteal artery was patent; this was likewise the case in regard to the portion of the femoral artery that came with the specimen. On histologic study, the vessels were found to have thickened walls, while some of them, particularly the popliteal artery, showed considerable medial sclerosis and intimal thickening, but none of the vessels in the regions examined showed evidences of thrombosis or recanalization. The muscles of the calf were extremely atrophic, while the muscles of the foot were somewhat infected.

When the muscles and periosteum were stripped from the amputated portion of the femur, enlargement of the longitudinally directed vascular canals was apparent, and thinning of the anterior portion of the cortex was obvious. When this bone was opened longitudinally, it was seen that the marrow cavity was enlarged from the endosteal side; the spongy trabeculae were definitely thin, and the marrow was fatty. Longitudinal sectioning of the tibia revealed atrophy in its upper third; the spongified diaphyseal cortex measured as much as from 10 to 12 mm. in thickness. The astragalus and calcaneus on section were atrophic and fatty. The toes showed gangrene and infection of the soft tissues and osteomyelitis and necrosis of the phalanges and possibly of the heads of the metatarsal bones.

Histologic examination of the femoral cross-sections demonstrated widespread aseptic necrosis; the original compacta (from periosteal to endosteal surfaces) was almost entirely dead. Some revascularization of the dead bone was in evidence, and as a result numbers of haversian canals were much enlarged; through fusion, some of the enlarged ones had produced wide haversian spaces; the widened, revascularized canals and spaces were lined by newly deposited bone and were filled with a loosely cellular connective tissue containing numerous blood channels (fig. 11 *A* and *B*). Extensive necrosis of the compacta was likewise apparent in tibial cross-sections, the innermost portions staining most poorly; resorption and revascularization were occurring from the periosteal side. The fatty marrow was edematous.

On histologic section the calcaneus evidenced extensive necrosis of the trabeculae and degeneration of the associated fatty marrow; however, evidences of revascularization of the marrow were to be found. The revascularized marrow contained deposits of new bone on the walls of some of the trabeculae; other trabeculae seemed to have undergone revivescence as a result of the revascularization. Here and there, the fragmentary formation of connective tissue bone in the marrow was noticeable. To a great degree, the astragalus illustrated similar microscopic pictures. While its articular cartilage still showed nuclear staining, the thick subchondral trabeculae were for the most part completely necrotic. Revascularization of the astragalus was in progress; some of the original trabeculae were in the process of resorption, and some of the necrotic marrow was being invaded by considerable granulation tissue.

The metatarsal bones were virtually completely necrotic, but regeneration was in progress, particularly from the periosteal side; new blood vessels and connective tissue had led to enlargement of existing vessel canals and erosion of the subperiosteal bone. Likewise, slight revascularization of the necrotic marrow had occurred, with the appearance of numerous new vessels in certain portions. The

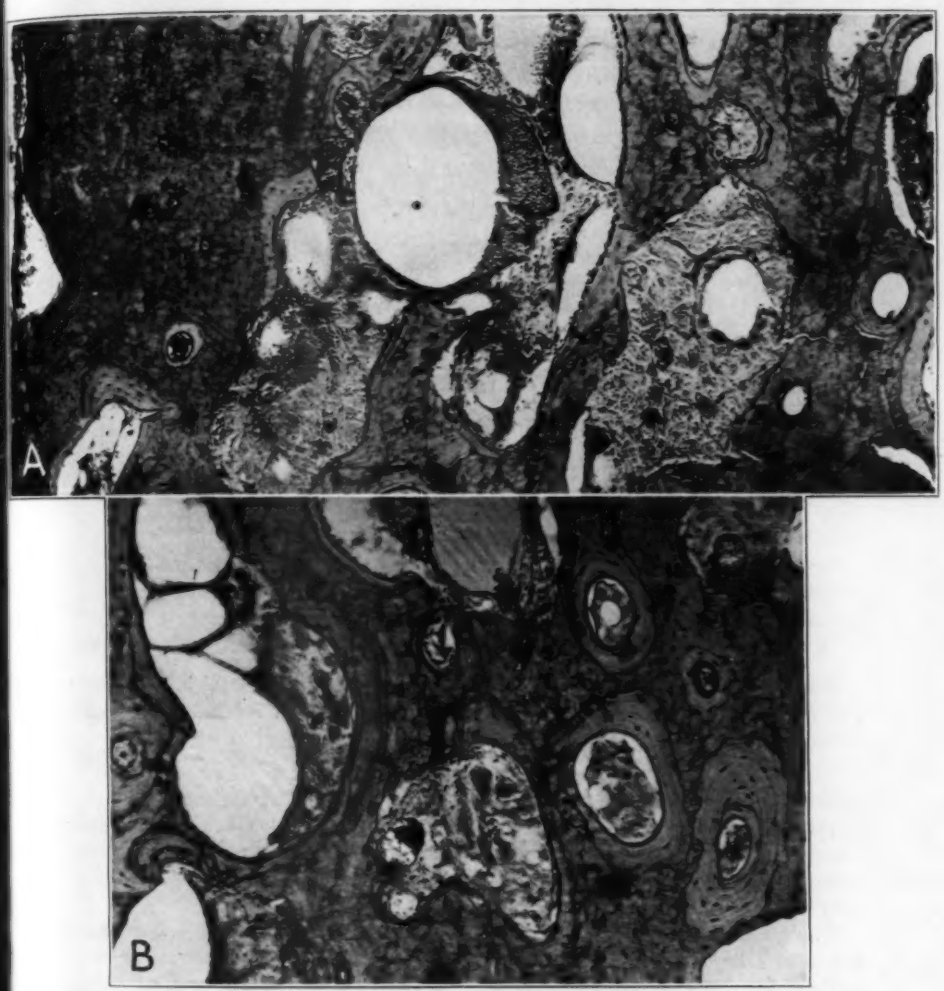

Fig. 11.—*A*, the femoral cortex in cross-section, demonstrating revascularization of dead bone; the haversian canals are enlarged; through fusion, wide haversian spaces have appeared. Much of the bone between these spaces was dead. It is plainly evident why the roentgenogram of the femur shows marked rarefaction (fig. 9); × 30. *B*, a higher magnification of an area represented in figure 11 *A*. The enlarged spaces are lined by newly deposited bone and are filled by loosely cellular connective tissue containing numerous newly formed blood channels; × 150.

articular cartilages of these bones were, on the whole, well retained (fig. 12). The phalanges demonstrated similarly that the orginal bone had undergone extensive or complete necrosis and that revascularization was actively in progress. The microscopic changes in the bones of the feet made explicable the roentgenographic appearances; the linear and oval shadows of increased permeability to light were the result of the resorption of the originally necrotic bone.

However, when revascularization, resorption and osseous transformation are slow in appearing or do not proceed to a considerable degree before amputation is performed, the roentgenogram of a gangrenous extremity may show essentially negative results, although bone necrosis may be widespread. This is confirmed by the examination of the right foot and leg in the following case:

Case 7.—A man, aged 26, was apparently entirely well until five weeks before admission to the hospital; at that time, cough and fever appeared. Two weeks before admission, he suddenly felt that his right foot was numb, cold and heavy,

Fig. 12.—The necrotic and rarefied cortex of the fifth metatarsal bone is shown. The cortex is thin, and the enlarged spaces are filled with inflammatory exudate (compare with figure 1); × 30.

without attendant pain; the toes also blanched. At admission, the toes of the right foot were black, and there were two red-black areas on the leg with lymphangitis; a blood culture was sterile; the blood sugar was normal. Amputation was performed two weeks after admission, or one month following the onset of the symptoms in the extremity.

The specimen consisted of the lower 6 inches (15 cm.) of the femur and the leg, and foot; a dry gangrene involving all of the toes and extending ventrally to the heel and dorsally over half of the surface of the foot was revealed. On the dorsum of the foot there was a line of demarcation above which the tissues were not black but discolored red; at the line the skin was interrupted. Posteriorly, the gangrene extended up from the heel to about the middle of the leg, where there was a sharp dividing line; at this line the skin was again interrupted. The demarcating line observed exteriorly was likewise seen in the muscles of the leg; the muscle in the gangrenous area was grossly degenerated and disorganized; in certain zones it was greenish and in others hemorrhagic, while that above the gangreous level retained the pink color. Some of the popliteal vessels were occluded by relatively fresh thrombi, which extended into the posterior tibial vessels; the anterior tibial

vessels, wherever traced, were found to be free from thrombi; no pockets of pus were found between any of the muscle bundles, although the tissues of the leg and foot had a foul odor.

Histologic study of the vessels demonstrated that the oldest process was in the posterior tibial artery; in this vessel there was evidence of complete recanalization of an organized thrombus. The sections further disclosed that the popliteal artery was more recently plugged; there were only slight organization and evidence of recanalization. Furthermore, the popliteal and posterior tibial veins were also thrombosed, and organization of the thrombi with recanalization was advanced in the posterior tibial tributaries. The histologic examination materially aided in interpreting the clinical phenomena that had occurred: First, there was closing of the posterior tibial artery by a thrombus; by then an adjustment period of about two weeks elapsed, and a phlebitis appeared. The phlebitis was migratory, and there was further extension of the arterial occlusion, resulting in the gangrene of the toes evident on admission of the subject. Finally, a spreading infection with lymphangitis necessitated amputation before the appearance of frank pus.

The soft tissues were dissected from the bones, and these were examined by roentgen rays. It was surprising to find that in spite of the extensive changes in

Fig. 13.—Roentgenogram of a sagittal section of the foot of a young man, aged 26, who suffered from acute arterial occlusion. The soft tissues of the foot showed extensive gangrene. None of the bones demonstrated are roentgenographically abnormal.

the soft tissues of the foot, the bones appeared roentgenographically normal; they also cut with normal resistance (fig. 13). The roentgenogram of the tibia disclosed a cortex of normal thickness, but there was slight rarefaction in portions of it, which was definitely the result of enlargement of vessel canals; the upper and lower ends of this bone showed no roentgenographic abnormalities. The fibula was likewise roentgenographically normal.

Further gross examination of the bones revealed no striking abnormalities, except that the marrow of the navicular bone was greenish yellow; the marrow of the cuboid was partly hemorrhagic; the marrow of the phalanges of the large toe was much discolored by blood; the same discoloration, to a lesser degree, was to be observed in the marrow of the first metatarsal bone; the condition in the other toes was comparable to that in the large toe. The other bones presented nothing abnormal in the gross, except that the marrow of the lower ends of the tibia and fibula was somewhat injected.

The histologic examination of the terminal phalanx of the large toe disclosed that its basal half was completely necrotic; this necrosis involved the articular

cartilage, medullary fat and surrounding soft tissues. However, the most distal half of the bone showed retention of the bone cell nuclei in most of the cortical area and in the spongy trabeculae, although the bone cell nuclei were pyknotic. This was entirely in keeping with the conditions in the surrounding soft tissue, which demonstrated a considerable number of staining nuclei and numerous dilated and engorged vascular channels—apparently of some nutritional potency. The proximal phalanx was virtually entirely necrotic, this being so with regard to the articular cartilages, the marrow and the spongy and cortical bone. In neither the distal nor the proximal phalanx was there evidence of revascularization of the bone or marrow; the necrotic bone represented the original bone without structural modification; the nuclei retaining stainability were those situated fortunately so as to receive nourishment. With regard to the first metatarsal bone, the conditions were practically identical: The marrow, cortex and spongy bone throughout were dead, and there was no revascularization. The histologic study of these bones clarifies the significance of the apparently normal roentgenographic appearance; the bones had died without any modification of their density, thereby casting the same shadow that they would have cast during life.

Roentgen examination of the other bones of the foot also for the most part gave negative results, but histologic study disclosed necrosis of the osseous and marrow tissue of these tarsal bones or of their parts that were surrounded by necrotic soft tissue. Wherever infection was superimposed, the necrosis was more pronounced. As observed in the large toe, there was no significant evidence of revascularization, resorption or osseous transformation in the necrotic zones. The tibia and femur, on histologic examination, reflected the same general observations.

SUMMARY AND CONCLUSIONS

The object of this work was to inquire into the nature of the microscopic changes occurring in the bones of gangrenous extremities resultant from vascular occlusion; particular attention was paid to the state of the bones at some distance above the level of gangrene and infection. Another phase of the investigation had special emphasis—the correlation of the gross and microscopic changes with any changes revealed on roentgenographic study of these bones. Apparently, Mueller alone had made somewhat similar histologic studies, in which he stressed extensive necrosis of the cells of the cortical interstitial lamellae as the only direct effects of circulatory disturbance due to arteriosclerosis. Undoubtedly the cells of the cortical interstitial lamellae have a marked tendency to die. Even in the absence of gangrene, this predisposition was evidenced in femoral cross-sections of our control specimens. These controls were taken from patients ranging from 8 to 62 years of age, who died from various causes. Thus, this tendency toward degeneration and death of the cells of deeply situated lamellae of compact bone is to be considered a normal characteristic, progressively increasing with age; in arterio-

sclerosis with gangrene it is more marked in the bone high above the gangrenous level; roentgenographically, this feature alone does not result in the appearance of abnormal shadows of bone.

When chronic vascular disease has persisted for any length of time before gangrene evolves, the marked and native disposition toward the development of collateral circulation frequently reduces to secondary importance the vascular obstruction factor per se as regards the production of changes in the bone. Although therapy may have for months staved off the necessity for amputation, the long interval of time has permitted such factors as infection, inactivity and so-called trophoneurotic influences to exert themselves on the bones. Thus, dependent on whether or not and to what extent these influences are brought into play, roentgenographic changes are present or absent in the bones, although they may show definite microscopic changes (particularly, extensive death of the interstitially placed bone). Six specimens of chronic vascular disease with gangrene illustrated the absence of specific and characteristic roentgenographic changes as a result of chronic vascular obstruction. This study marked more clearly the need for understanding the microscopic changes in order to interpret properly any roentgenographic evidence of changes in the bone. It was pointed out that the bones of a gangrenous toe, although appearing roentgenographically normal, may on histologic examination evidence osteomyelitis; the absence of periostitis in the roentgenogram is explicable by the devitalization of the soft tissues about the bones. Furthermore, if a devitalized bone is revascularized through circulatory readjustments, the resorption and reconstruction will be demonstrated roentgenographically by punctate shadows of increased permeability; they are the result of enlargement of earlier vascular canals and cortical erosion (particularly from the periosteal side). Diabetic patients with arteriosclerosis and gangrene are so predisposed to extensive infection that their necrotic bones, becoming potentially infected sequestrums, show less tendency toward revascularization.

One case is reported of high, acute, vascular occlusion with a long delay in the appearance of gangrene. Collateral circulation was adequate to prevent gangrene, though not sufficient for normal nutrition. Roentgenograms of the bones of the extremity five months after the onset of the vascular occlusion revealed extensive changes; there were areas of rarefaction disseminated throughout and exhibited in round or somewhat elongated shadows, everywhere less dense than normal. Histologic examinations of the bone high above the gangrenous level disclosed the

existence of widespread, aseptic necrosis, the original compacta of the femur being almost entirely dead. Revascularization of the dead bone was in evidence and therefore numbers of haversian canals were greatly widened, still more so through the fusion of some of them; the new spaces were lined by newly deposited bone and contained loosely cellular connective tissue with numerous blood vessels. Extensive necrosis of the compacta of the other bones was likewise in evidence. The roentographic appearance here was essentially due to the revascularization of dead bone.

SEQUENCES OF EXPERIMENTAL INFARCTION OF THE FEMUR IN RABBITS

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A number of lesions, etiologically obscure but with certain characteristics in common, have been described in various bones. The onset and clinical progress are insidious and may or may not be associated with trauma. In these lesions there is a gradual and progressive destruction of the tissues of the bone, as demonstrated in roentgen films and by examination of tissue. The parts involved are almost always in an epiphysis or in epiphyseal cartilage, and ultimately a deformity of the bone results. These various lesions have been designated osteochondritis, anemic infarction, epiphysitis or aseptic necrosis of bone, terms which imply some vascular or nonspecific disorder not clearly understood. Among the more important specifically named disturbances of this group are: aseptic or anemic necrosis of the head of the femur, radius or humerus or distal epiphysis of the femur; König's osteochondritis dissecans of the medial condyle of the femur; osteochondritis deformans juvenilis of Perthes, Legg and Calvé; Osgood-Schlatter's disease of the tibial tubercle; Sudeck's acute atrophy of bone; necrosis of the tarsal navicular bone (Köhler's disease), of the bodies of the vertebrae (Kümmell's disease), of the head of the metatarsal bones (Freiberg's disease, also described by Köhler) and of the carpal semilunar bone (Kienböck's disease), and occasional foci in many other bones, particularly of the lower extremity.

The cause of these necroses is not understood, and the etiologic factors concerned have been hypothecated rather than actually demonstrated in the diseased tissues. In view of the occasional bilateral occurrence and the incidence of these lesions of bone in several members of a family, a hereditary tendency is assumed by some to be a factor (Bernstein).[1] Since these lesions are frequently present in a bone near a joint, the trauma of weight bearing and muscle tension have been

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1. Bernstein, M. A.: Osteochondritis Dissecans, J. Bone & Joint Surg. **7**:319, 1925.

considered important (Geyman,[2] Kappis [3] and Dürig [4]), and many consider that external trauma, probably associated with a local vascular disturbance, is the chief factor. The most plausible explanation yet offered seems to be a primary alteration of the normal nutrition in a region of bone followed by or associated with trauma or a mild infectious agent.

Following an exhaustive study of the various forms of necrosis of bone, all of which he considered to be fundamentally alike, Axhausen [5] stated that these are bland anemic infarcts of bone produced by mycotic emboli. This opinion is hypothecated, because Axhausen assumed that attenuated organisms are present. The possibility of a vascular nutritional disturbance being an important primary etiologic factor has gained considerable credence and has been emphasized in the more recent clinical and experimental studies. Phemister [6] supported the theory of infarction, but considered this alone insufficient to produce the marked changes usually present. Phemister, Brunschwig and Day [7] cultivated successfully a streptococcus from the necrotic marrow tissues of two bones with Kienböck's disease, one with Perthes' disease and one with Köhler's disease. Attempts to reproduce such lesions by the intravenous injection of pyogenic organisms were unsuccessful. In his original report on osteochondritis dissecans, König [8] considered trauma alone insufficient to produce the changes and believed that the loose bodies in the knee joint were probably sequestrated infarcted bone. In a symposium of twelve articles [9] by Legg, Calvé, Moreau and others, the general opinion was expressed that the principal site of osteochondritis juvenilis is the epiphyseal line and that the etiology is unknown, but is probably associated with a mild infection or a disturbance of circulation. In a more recent survey of opinions, Perthes [10] concluded that internal

2. Geyman, M. J.: Osteochondritis Dissecans, Radiology **11**:315, 1928.

3. Kappis, M.: Osteochondritic Dissecans, Deutsche Ztschr. f. Chir. **171**:13, 1922.

4. Dürig, A.: Beitrag zur Aetiologie der Köhlerschen Krankheit, München. med. Wchnschr. **70**:362, 1923.

5. Axhausen, G.: Ueber anämische Infarkte am Knochensystem und ihre Bedeutung für die Lehre von den primären Epiphyseonekrosen, Arch. f. klin. Chir. **151**:72, 1928.

6. Phemister, D. B.: Newer Knowledge of Pyogenic Infection of Bone, Proc. Inst. Med. Chicago **7**:169, 1929.

7. Phemister, D. B.; Brunschwig, A., and Day, L.: Streptococcal Infections of the Epiphyses and Short Bones, J. A. M. A. **95**:995 (Oct. 4) 1930.

8. König, F.: Ueber freie Körper in den Gelenken, Deutsche Ztschr. f. Chir. **27**:90, 1887.

9. Symposium: Legg, A.: Arch. franco-belges de chir. **25**:585 (April) 1922. Calvé, J.: Arch. franco-belges de chir. **25**:592 (April) 1922. Moreau, J.: Arch. franco-belges de chir. **25**:652 (April) 1922.

10. Perthes, G.: Ueber Osteochondritis deformans coxae, Klin. Wchnschr. **3**: 513, 1924.

factors cause a change in the epiphyseal cartilage of the head of the femur, and the accidental lesion of a blood vessel leads to necrosis. Hirsch and Ryerson,[11] in a report on marked necrosis of the distal epiphysis of the femur, emphasized the long duration and progressive destruction of the bone without attempt at repair in these lesions. They believed the primary cause to be one of vascular occlusion. The anatomic position of metastatic subchondral and metaphyseal foci of osteomyelitis is often attributed to occlusion of end-arteries by infected emboli. According to Nussbaum,[12] the diaphysis of long bones can resist such foci of infection because of an abundant collateral blood supply.

There are many reports and discussions on so-called aseptic necrosis of the head of the femur associated with or following dislocation of the head or intracapsular fracture of the neck of the femur. Some necroses are also associated with so-called slipping of the upper epiphysis of the femur. The consensus is that such necrosis is the result of a nutritional disturbance, usually from injury to the blood supply carried in the ligamentum teres femoris.

Many physiologic and anatomic factors must be considered in order to appreciate the full significance of necrosis in bone and the great difficulty attending its study. Important among these are: (1) the general circulatory pattern, (2) the relative importance for normal nutrition of the various sources of blood and (3) the presence or absence of end-arteries and anastomoses. Because of the great vascularity of bone, experimental division of a vessel does not, except in isolated instances, simulate occlusion of the endings of that vessel by emboli.

The evidence at present favors the opinion that the bone marrow tissues in mammals have a closed vascular system, that is, arterial and venous blood flow in defined channels with distinct endothelial linings (Sabin [13]), and that some regions are different from the general pattern because they are nourished by a certain vessel or group of vessels of common origin. There are four chief sources of arterial blood in long bones: (1) the principal and occasional accessory nutrient arteries to the shaft; (2) small vessels that pierce the cortex to enter the metaphyseal ends of the shaft; (3) periosteal twigs that enter the cortical bone, and (4) small but distinct epiphyseal vessels, including those of the femur that are carried by the ligamentum teres and those that enter at the attachment of a joint capsule. The ramification and anastomosis of these vessels in growing bones probably is altered by the presence

11. Hirsch, E. F., and Ryerson, E. W.: Necrosis of the Distal Epiphysis of the Right Femur, J. A. M. A. **93**:679 (Aug. 31) 1929.

12. Nussbaum, A.: Beziehungen der Knochengefässe zur akuten Osteomyelitis, Zentralbl. f. Chir. **49**:700, 1922.

13. Sabin, F. R.: Bone Marrow, Physiol. Rev. **8**:191, 1928.

of epiphyseal cartilage plates. Johnson [14] studied the relative importance of these systems to the normal nutrition of the shaft of the tibia in dogs by determining the rate of osseous repair in drill holes and the distribution of india ink in the medullary tissues after interruption of one or two sources by division of the vessels. He concluded that the nutrient artery supplied the medulla and the inner portion of the cortex and was sufficient alone to maintain normal viability of the tissues of the shaft; that the metaphyseal vessels would supply enough blood to the shaft to prevent necrosis but not to promote repair, and that the periosteal twigs supplied only the outer two thirds or one half of the cortex and formed very few anastomoses with the medullary channels. He did not consider the age of the animals and the possibility of epiphyseal collateral circulation to the shaft. Using the experimentally fractured fibulas of dogs, Pearse and Morton [15] observed no impairment in healing after division of the nutrient vessel, owing to rapidly developed collateral circulation. Moore and Corbett,[16] however, could not obtain healing in experimental fractures after the nutrient artery was ligated. On the other hand, according to McWilliams,[17] Kolodny,[18] Haldeman [19] and Gallie and Robertson,[20] the periosteal blood supply to the shaft is most important. These divergent views indicate that more attention should be given to the collateral circulation and that experimental procedures more than interruption of the arteries must be used. Brunschwig [21] produced infarction of the tibia of young dogs by stripping the entire shaft of its periosteum and presumably tearing the nutrient artery. This did not occur in adult animals, which demonstrates the important collateral circulation to the shaft that develops from the epiphyses after the cartilage lines close. Continuity of epiphysis and diaphysis, established by obliteration of the epiphyseal lines, may account for the infrequency of foci in adult bones comparable to metaphyseal foci of infection and necrosis in growing bones.

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14. Johnson, R. W., Jr.: A Physiological Study of the Blood Supply of the Diaphysis, J. Bone & Joint Surg. **9**:153, 1927.

15. Pearse, H. E., Jr., and Morton, J. J.: The Influence of Alterations in the Circulation on the Repair of Bone, J. Bone & Joint Surg. **13**:68, 1931.

16. Moore, J. E., and Corbett, J. F.: Studies on the Function of the Periosteum, Surg., Gynec. & Obst. **19**:5, 1914.

17. McWilliams, C. A.: The Periosteum in Bone Transplantations, J. A. M. A. **62**:346 (Jan. 21) 1914.

18. Kolodny, A.: The Periosteal Blood Supply and Healing of Fractures, J. Bone & Joint Surg. **5**:698, 1923.

19. Haldeman, K. O.: The Rôle of the Periosteum in Healing of Fractures: Experimental Study, Arch. Surg. **24**:440 (March) 1932.

20. Gallie, W. E., and Robertson, D. E.: The Repair of Bone, Brit. J. Surg. **7**:211, 1919.

21. Brunschwig, A.: Experimental Infarction of Bone Marrow, Proc. Soc. Exper. Biol. & Med. **27**:1049, 1930.

The importance of the ligamentum teres to a normal blood supply in the head of a femur depends on the ability of that bony epiphysis to develop collateral circulation. Müller,[22] Freund,[23] Speed,[24] Wolcott,[25] Santos,[26] Chandler and Kreuscher[27] and many others, after clinical studies and gross and microscopic examination of the ligamentum teres in cadavers and in tissues removed at operation, stress its need for the prevention of necrosis of the head of the femur such as may follow dislocation or fracture. Kolodny[28] took another view, since he demonstrated the intracapsular periosteum and periosteal blood supply of the neck of the femur to be the same as elsewhere. If the proximal epiphyseal line is closed so that there is medullary continuity between the head of the epiphysis and the shaft, destruction of the ligament should do no harm. If, however, this continuity is interrupted above the brim of the articular cartilage, whether the line is open or closed, and the ligamentum teres is ruptured, the proximal fragment will be severed completely from its blood supply. Thus, necrosis of the head of the femur may occur at any age and should not be confused with osteochondritis juvenilis, which is primarily a disturbance in the open proximal epiphyseal line of growing bones.

Without good experimental evidence, end-arteries are assumed to be present beneath open epiphyseal plates, and articular cartilages and medullary tissues otherwise are considered to have a dense meshwork of active and potential arterioles and capillaries. This is probably the basis for the frequent occurrence of metaphyseal and subchondral metastatic infections and necroses. According to Johnson and Kolodny, Lexer and Kuliga[29] thought that the branches of the nutrient artery

22. Müller, W.: Experimentelle Untersuchungen über Nekrosen und Umbauprozesse am Schenkelkopf nach traumatischen Epiphysealsungen und Luxationen und ihre klinische Bedeutung, Beitr. z. klin. Chir. **132**:490, 1924.

23. Freund, E.: Zur Frage der aseptischen Knochennekrose, Virchows Arch. f. path. Anat. **261**:287, 1926.

24. Speed, K.: Fracture of the Neck of the Femur, Ann. Surg. **96**:951, 1932.

25. Wolcott, W. E.: Circulation of the Head and Neck of the Femur: Relation to Nonunion in Fractures of the Femoral Neck, J. A. M. A. **100**:27 (Jan. 7) 1933.

26. Santos, J. V.: Changes in the Head of the Femur After Complete Intracapsular Fracture of the Neck: Their Bearing on Nonunion and Treatment, Arch. Surg. **21**:470 (Sept.) 1930.

27. Chandler, S. B., and Kreuscher, P. H.: A Study of the Blood Supply of the Ligamentum Teres and Its Relation to the Circulation of the Head of the Femur, J. Bone & Joint Surg. **14**:834, 1932.

28. Kolodny, A.: The Architecture and the Blood Supply of the Head and Neck of the Femur and Their Importance in the Pathology of Fractures of the Neck, J. Bone & Joint Surg. **7**:575, 1925.

29. Lexer, E., and Kuliga, P.: Untersuchungen ueber Knochenarterien mittelst Roentgenaufnahmen injizierter Knochen und ihre Bedeutung fuer einzelne pathologische Vorgaenge am Knochensysteme, Berlin, A. Hirschwald, 1904.

extend to but do not pierce the open epiphyseal lines or anastomose with the vessels of that region entering through the cortex until after growth has ceased. It seems logical to consider that such a region depending on one source of blood is, in reality, a region with so-called end-arteries. Kolodny, however, stated that some of these metaphyseal branches of the nutrient artery pierce the epiphyseal line and enter the bony epiphysis (described for the head of the femur), and thus the metaphysis may draw blood from the epiphysis. Freiberg [30] called attention to the arteria genu media which arches over the posterior central ligament and the internal condyle of the femur. He stated that it is frequently terminal and if blocked will produced osteochondritis dissecans, as described by König.

Attempts to produce infarcts of bones experimentally in animals have aided little in understanding the clinical disorders mentioned. These attempts, however, have emphasized the necessity of adequate nutrition for normal vitality. Axhausen [31] produced necrosis of bone by the use of heat, cold and tincture of iodine, and Phemister [32] obtained similar death of tissues and reactive changes with radium. Bancroft [33] studied necrosis, sequestration and involucrum formation in the humerus of dogs following intramedullary injections of croton oil. He emphasized the importance of the blood supply to the regeneration of bone. Using the head of metatarsals of growing dogs, Sacerdote [34] produced marked necrosis and deformity by removing the periosteum from a fractured segment. With removal of the periosteum or by fracture alone, the vascular changes and the resulting necroses were much less. Nussbaum [35] demonstrated necrosis and almost complete restoration of epiphyseal ossifying centers after destruction of the blood supply to the epiphyses. Partial necrosis and slight flattening of the head of the femur near the fovea were produced in young goats by Graham,[36] who attempted to reproduce osteochondritis juvenilis by destruction of the

30. Freiberg, A. H.: Osteochondritis Dissecans, J. Bone & Joint Surg. **5**: 3, 1923.

31. Axhausen, G.: Knochennekrose und Sequesterbildung, Deutsche med Wchnschr. **40**:111, 1914.

32. Phemister, D. B.: Radium Necrosis of Bone, Am. J. Roentgenol. **16**: 340, 1926.

33. Bancroft, F. W.: Bone Repair Following Injury and Infection, Arch. Surg. **5**:646 (Nov.) 1922.

34. Sacerdote, G.: Sulle consequenze di interruzioni circolatorie e di fratture nelle epifisi di animali in accrescimento, Chir. d. org. di movimento **16**:291, 1931.

35. Nussbaum, A.: Die Arteriellen Gefässe der Epiphysen des Oberschenkels und ihre Beziehungen zu normalen und pathologischen Vorgängen, Beitr. z. klin. Chir. **130**:495, 1924.

36. Graham, R. V.: Experimental Considerations in Perthes' Disease (Division of Ligamentum Teres), M. J. Australia **1**:207, 1930.

ligamentum teres. By a similar procedure, Zemansky and Lippmann [37] caused considerable necrosis of bone and medullary tissues, flattening of the weight-bearing portion of the head and coxa vara deformity of the neck of the femur in young rabbits. They considered these changes to be very similar to those in Perthes' disease. Such changes did not follow interference with the ligamentum teres in adult rabbits, and from this they concluded that the ligament was not important for the nutrition of the femoral head after the cessation of growth. Stewart [38] could demonstrate no consistent changes in rabbits after division of the ligamentum teres. During an attempt to produce experimental arthritis in rabbits by the intravenous injection of pyogenic organisms, Jackson [39] demonstrated wedge-shaped infarcts of bone that were situated in the metaphyses with their bases close under the epiphyseal cartilage. This indicates that there are probably end-arteries in the metaphyses and that they may be occluded by emboli.

In view of the paucity of experimental studies concerned primarily with necrosis and repair of bone, it seemed profitable to accumulate further data on the circulatory pattern of bone and the nature of infarcts in this tissue. Since simple ligation of vessels alone is unsatisfactory, because of the rapid formation of collateral circulation within the medullary tissues and outside the cortex, bland emboli were used so that small vessels would be occluded. Such a method also might elucidate the relative importance of the various sources of blood supply to a given portion of bone by a study of the nature and extent of the necrosis produced. If infarcts result, then a more applicable approach to the study of clinical entities involving necrosis has been formulated.

BLOOD SUPPLY TO THE FEMUR IN THE RABBIT

The femur in the rabbit has the usual small epiphyseal arterial twigs and periosteal blood supply. In addition, and far more important for normal nutrition, there are three principal vessels, all indirectly branches of the femoral artery. Two of these are branches of the profunda femoris which, in the rabbit, leaves the femoral artery at about the inguinal ligament and courses medially and downward. The first nutrient vessel leaves the profunda about 1.3 cm. from its origin (adult animal) and courses backward, inward and slightly upward to enter a large acetabular foramen in the ischium and become continuous with

37. Zemansky, A. P. Jr., and Lippmann, R. K.: The Importance of the Vessels in the Round Ligament to the Head of the Femur During the Period of Growth and Their Possible Relationship to Perthes' Disease, Arch. Path. **7**:187 (Jan.) 1929.

38. Stewart, W. J.: Aseptic Necrosis of the Head of the Femur Following Traumatic Dislocation of the Hip Joint, J. Bone & Joint Surg. **15**:413, 1933.

39. Jackson, L.: Experimental Streptococcal Arthritis in Rabbits, J. Infect. Dis. **12**:364, 1913.

the vessels of the ligamentum teres. The second nutrient division arises 1 mm. or so distal to the first. It passes posteriorly to the medial edge of the lesser trochanter and then laterally across the lesser trochanter and posterior surface of the proximal end of the femur to enter the inferior angle of the trochanteric fossa with the tendon insertions of the short rotator muscles. Another, less significant, branch of the profunda femoris extends upward and backward to wind about the joint in the capsule near its attachment to the femur. This vessel probably supplies numerous small twigs to the adjacent bone and the greater trochanter. The third important vessel to the femur is the nutrient artery of the shaft which arises from the lateral circumflex artery near its origin from the femoral artery. It courses downward and backward to enter the nutrient foramen of the shaft on its medial surface near the linea aspera. These vessels probably vary in their details and anastomose freely with other vessels. In the many histologic preparations of the femur examined, only one epiphyseal vessel was noted to pierce an epiphyseal cartilage plate and enter the metaphysis. This small vessel, occasionally present in the plane of the sections examined, entered the upper end of the shaft from the greater trochanter and was constant in its position. Small periosteal twigs were more numerous where muscles and tendons attached, particularly on the posterior surface of the distal end of the shaft, and where the capsule of the hip joint inserted about the head of the femur. According to Piney,[40] the entire bone marrow of rabbits is cellular and penetrated by small vascular channels which, in long bones, branch from a central artery in the axis of the tissues.

EXPERIMENTAL METHODS

Infarction by embolism was produced by injecting a 2 per cent suspension of charcoal in physiologic solution of sodium chloride containing 5 per cent acacia into the nutrient arteries of the femur.[41] These particles of carbon were of the size that would pass through a sieve of 200 but not of 300 mesh per inch. Through an incision on the medial aspect of the thigh the femoral artery was exposed and ligated about 1 cm. distal to the origin of the lateral circumflex artery. The femoral artery proximal to the lateral circumflex artery and the lateral circumflex artery distal to the origin of the nutrient artery to the shaft of the femur were temporarily occluded by lifting ligatures. Small subcutaneous and muscle branches were ligated and cut. From 0.8 to 2 cc. of the suspension of charcoal was then slowly injected retrogradely into the femoral artery above the distal permanent ligature with a small gage needle, and afterward a second ligature was placed above the opening made in the vessel. This pro-

40. Piney, A.: The Anatomy of the Bone Marrow: With Special Reference to the Distribution of the Red Marrow, Brit. M. J. **2**:792, 1922.

41. This method was used by Miller and Apfelbach in the infarction of renal glomeruli (Experimental Infarction of the Glomeruli in Dogs, Arch. Path. **4**: 193 [Aug.] 1927). Dr. Apfelbach loaned me some of his apparatus.

cedure directed the suspension into the nutrient artery of the shaft. Before the needle was removed, sufficient suspension was withdrawn into the syringe to prevent occlusion of the femoral artery by carbon. Similar injections were made also with the proximal temporary ligature of the femoral artery placed above the origin of the profunda femoris so that carbon was allowed to enter the proximal end of the femur and the innominate bone through the branches of the profunda. The femoral artery of several of the legs, used as controls, was ligated without the injection of charcoal, but no attempt was made to equalize weight bearing. It is difficult to evaluate the possibility of some periosteal infarction through small twigs of vessels receiving carbon. Benassi [42] ligated the femoral and iliac arteries and veins separately and together, in growing and adult rabbits, and Pearse [43] removed the entire femoral artery in dogs without producing any noteworthy nutritional disturbances or functional disability of the leg.

A second approach to the study of changes in the bone, resulting from interference with normal nutrition, was by interrupting, at the site of entrance to the bone, one or a combination of vessels known to be distributed to the marrow tissues of the femur. The nutrient artery to the shaft was ligated through a small incision on the medial aspect of the thigh. Access to the ligamentum teres and the small vessel that enters the proximal end of the femur through the trochanteric fossa was obtained through an incision placed posteriorly over the hip joint with the leg adducted and rotated inward. During manipulation of the ligamentum teres there was moderate trauma to the articular surfaces and capsule of the hip joint. In no instance was there intentional interference with the periosteal blood supply.

The studies reported were made on the femurs of forty-six rabbits from 3 weeks to 2 years of age maintained on stock ration of oats and hay. Operative manipulations were performed with aseptic precautions under local infiltration of procaine hydrochloride or general anesthesia induced by pentobarbital sodium. The femurs were removed for examination from twenty hours to one hundred and fifty days after operation, cut into three segments (proximal, middle and distal thirds) and fixed in a dilute solution of formaldehyde, U. S. P. (1:10). After decalcification by 4 per cent solution of nitric acid, the segments were split longitudinally in such a way that the surfaces made would be of maximum size. Longitudinal sections of these tissues for histologic examination were prepared by the pyroxylin (celloidin) method and stained with hematoxylin and eosin. As an added check on the source of arterial blood to different portions of the femur, lithium-carmine and india ink were injected intravenously into some of the animals before death. In addition to the usual examinations, such preparations were studied grossly according to color distribution and microscopically in unstained preparations.

RESULTS

The changes produced in the femurs of rabbits during a given period varied according to the age of the animals and the technical difficulties of injecting corresponding amounts of carbon in the same manner and probably also according to individual differences. Infarcts were readily

42. Benassi, E.: Lo sviluppo e trofismo dello scheletro degli arti in rapporto alla allacciatura dei vasi principali, Arch. ital. di chir. **28**:49, 1931.

43. Pearse, H. E., Jr.: An Experimental Study of Arterial Collateral Circulation, Ann. Surg. **88**:227, 1928.

produced by the injection of carbon alone, or in combination with rupture of an important nutrient vessel, but the necrosis was usually less marked and more poorly circumscribed when the circulation from one or more sources was interrupted external to the cortex without injection. The inability to control exactly the distribution of the carbon, owing to anastomoses of the nutrient vessels, and the possibility of infarction of soft tissues, particularly periosteum, are fully appreciated. It is also difficult to evaluate the effects of unequal weight bearing of the limbs. Practically all animals, however, behaved after operation much as before.

Fig. 1.—Necrosis and liquefaction of the distal epiphyseal cartilage of the right femur in a young (3 weeks) rabbit fourteen days after the injection of carbon into the nutrient artery to the shaft. The right femur is 4 mm. shorter than the left femur.

Definite gross external alterations in the size and the configuration of the femur were noted ten or more days after infarction. The cortical bone corresponding to the site of the infarcts was thickened, often porous, and its periosteal surface roughened, especially at the insertion of muscles and tendons. Other changes, present only in growing bones, were associated with the lack of continuity in the medullary circulation between the diaphysis and the epiphysis. Infarcts of the distal end of the shaft produced hypoplasia of ossification in the distal cartilage plate

amounting to as much as 4 mm. of growth in seventeen days (fig. 1), while infarcts of the proximal portion of the femur produced shortening because of interference with growth from the proximal epiphyseal line. When the head and neck were deprived of blood, the head became flat and broad so that its brim overhung the shortened neck, and the angle made by the neck and the shaft was more acute than normal (coxa vara), as in figure 2. There were complete necrosis and absorption of the head and neck in one growing animal examined thirty days after

Fig. 2.—Right and left femurs of a young rabbit one hundred and fifty days after division of the right ligamentum teres and the vessel that entered the trochanteric notch. The weight-bearing surface of the head of the right bone is flattened so that the edges overhang the neck, which is shorter than the left and makes a more acute angle with the shaft. The upper portion of the shaft of the right femur is bowed laterally, and there has been less growth here than in the left.

rupture of the ligamentum teres and the vessel that entered the trochanteric notch accompanied by considerable trauma to the bone and cartilage tissues of the head. When infarction of the entire shaft was produced by particles of carbon entering all of the nutrient vessels proximal to the distal epiphysis, the shaft tended to bow laterally, and

the head and neck rotated forward as though the entire shaft were twisted.

Surfaces made by splitting the femurs longitudinally after decalcification demonstrated certain noteworthy features. Infarcts produced by emboli injected through the nutrient artery of the shaft of growing bones were proportionately larger and extended to the regional cartilage plate, while those in adult bones extended only to within from 6 to 10 mm. of the obliterated growth line. The recent infarcts were dark red and poorly differentiated, while the older ones were demarcated from adjacent vascular marrow by centers of pale gray tissue of the nature of fat that had margins of a more fibrous texture. In these infarcts, the necrosis was more marked, and the junction of living and dead tissues was more distinct distal to the level of the nutrient foramen because of the more abundant smaller accessory nutrient vessels in the proximal portion of the shaft. The delimitation by anemia and necrosis was accentuated by the intravenous injection of lithium-carmine or india ink previous to killing the animals. Such infarcts did not follow interruption of the circulation outside the cortex except in one instance in which ligation of the nutrient artery to the shaft in a rabbit 3 weeks of age produced, in nine days, a wedge-shaped infarct in the center of the distal metaphysis. The base of this anemic region was at the cartilage plate, which was twice as wide as the corresponding plate of the other femur, as if there had been marked impairment to normal ossification of cartilage (fig. 3). It is significant that during these nine days the femur which had not been operated on outgrew the femur in which infarction had been produced by 2 mm. Metaphyseal infarcts produced by the injection of carbon caused similar hypoplasia of bone, but the epiphyseal lines in these femurs closed earlier than those of the control femurs. This difference in alteration of the growth line is based on sufficient nutritional disturbance to prevent ossification by ligation of a vessel contrasted with complete infarction, even of the proliferating cartilage, produced by the embolic occlusions of vessels (fig. 4). In another young rabbit the lateral half of the head of the epiphysis was an anemic infarct four days after charcoal had been introduced into the femoral artery in such a way that a portion was carried through the vessels of the ligamentum teres. The entire head was infarcted, and there was considerable deformity of it and of the neck in a growing rabbit examined thirty days after rupture of the ligamentum teres and injection of carbon into the nutrient vessel of the shaft. Similar but less marked anemic necrosis and deformity usually followed rupture of the ligamentum teres and the vessel entering the proximal end of the femur in the trochanteric notch. In one femur subjected to this procedure there were complete necrosis and absorption of the head and a portion of the neck. To corroborate the distribution of carbon and blood

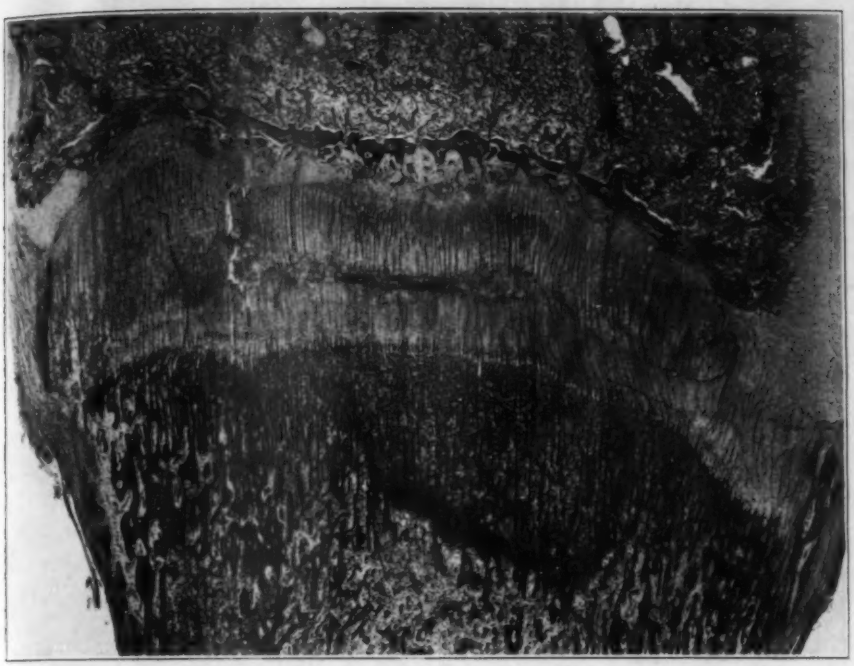

Fig. 3.—Inhibition of metaphyseal ossification and subsequent overgrowth of the distal epiphyseal cartilage plate in a femur of a young rabbit nine days after ligation of the nutrient artery to the shaft; × 15.

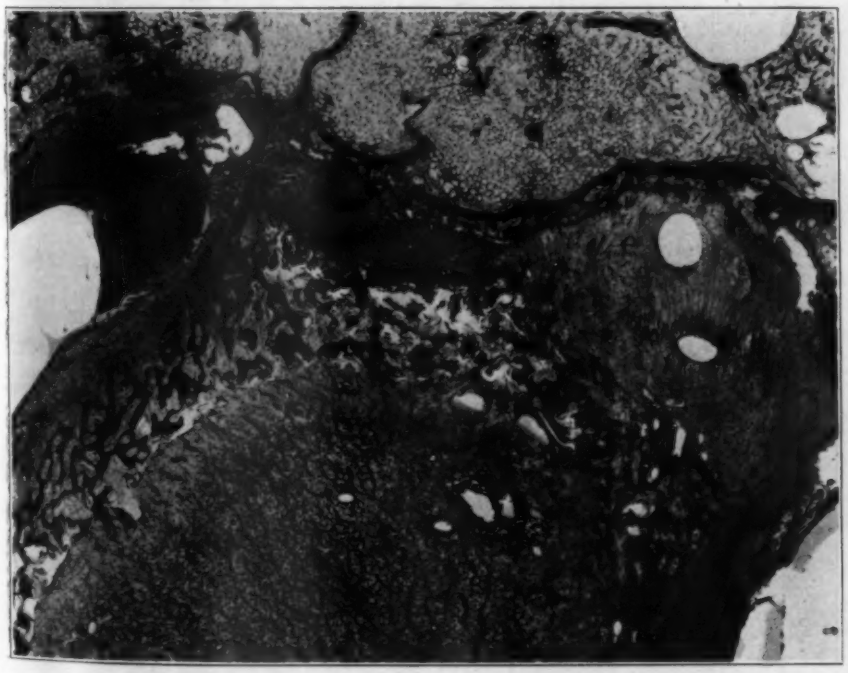

Fig. 4.—Necrosis and liquefaction of the distal epiphyseal cartilage plate in the femur of a young rabbit fourteen days after infarction by charcoal emboli; × 15.

supply through the ligamentum teres, histologic preparations of decalcified acetabula cut longitudinally demonstrated carbon and necrosis in the bone tissues of the ischium, but not in the portion of the ilium that goes into the formation of the acetabulum.

Histologically, infarcts produced by charcoal emboli, regardless of their situation and the reaction in and about these regions of necrosis, may be considered as a group, for they differ only in extent and in local opportunity for revascularization and ultimate replacement of tissue. The following summarizing description is confined chiefly to embolic infarcts of the shaft of the femur, since they occurred regularly and were of a fairly uniform pattern. In the medullary tissues infarcted for twenty hours there were diffuse hemorrhages, mainly in the center of the medullary canal and at the junction of the infarct and neighboring normal tissues. The marrow cells stained poorly, and there was beginning disintegration of tissue, particularly about small blood vessels occluded by the carbon (fig. 5). In some there were columns of epiphyseal cartilage cells, especially on the metaphyseal side of the epiphyseal plate, that had diminished or altered staining reactions. After two days the region of necrosis was well defined by its granular nature and the absence of cellular structure, usually more prominent in the center of the cavity of the infarcted bone. Within four days there was a diminished staining reaction of the endosteal bone in the center of the infarct, and some of the lacunae were empty. The inner surface of this compact bone was irregular and without the usual layer of osteoblasts. At the junction of the necrotic and noninfarcted medullary tissues there was considerable hyperemia with a beginning sequestration, as evidenced by an increased fine fibrillar stroma. If the infarct included a metaphyseal end of the shaft, the reactive changes developed from the angle of the epiphyseal line and the cortex alone and not from the cartilage. For this reason, and because of the avascularity of articular cartilage, infarcts of the head of the femur were more or less isolated, and they produced less active regenerative changes.

Infarcts of nine days' duration (fig. 6) demonstrated a marked reparative reaction to the dead tissues. The limiting walls of the infarcts were more dense vascular fibrous connective tissue, and extending into them from the endosteum were small spicules of new bone. These partitions of the medullary cavity resembled nonspecific chronic granulation tissue, and they were cone-shaped with the tip pointed away from the infarct as though there were more destruction in the center of the cavity than along the cortical bone. This arrangement was probably due to the diagonally downward and outward branching of the central nutrient vessel in the shaft and to the greater blood supply of the marrow along the endosteum. After fourteen days the inner one fourth to

Fig. 5.—Hemorrhages and necrosis of the marrow tissues in the proximal end of a femur four days after infarction by charcoal emboli; × 15.

Fig. 6.—Zone of reaction with beginning proliferation of endosteal new bone and spicules of dead bone about necrotic marrow tissues nine days after infarction by charcoal; × 15.

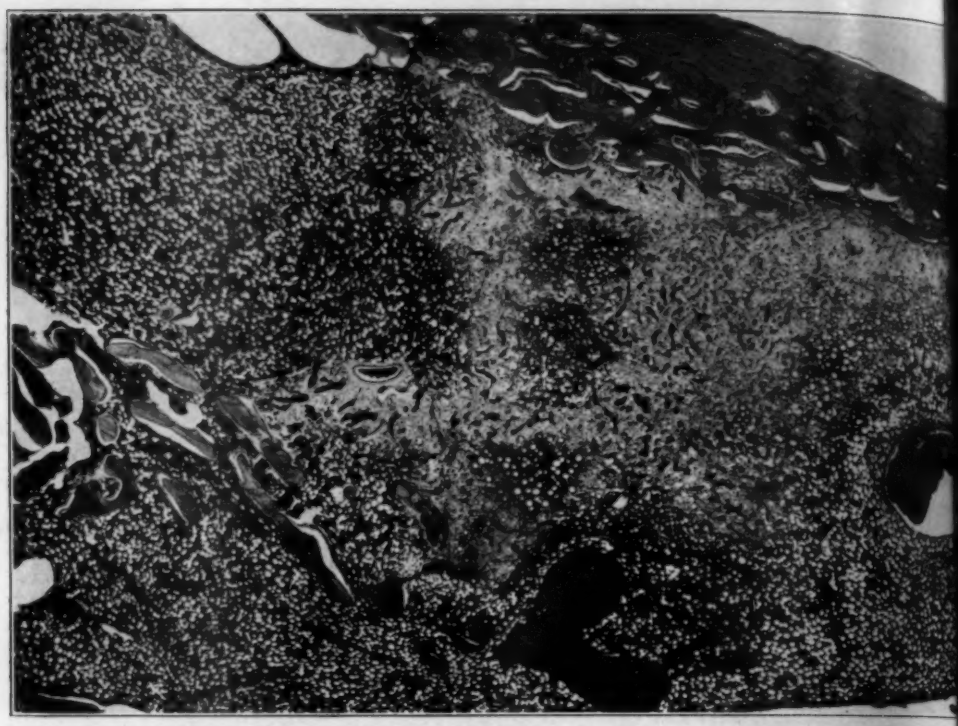

Fig. 7.—Revascularization of an infarcted region in the proximal end of the femur fourteen days after the injection of charcoal. Necrotic trabeculae and endosteal bone are being replaced by new bone. Reduced from a magnification of × 15.

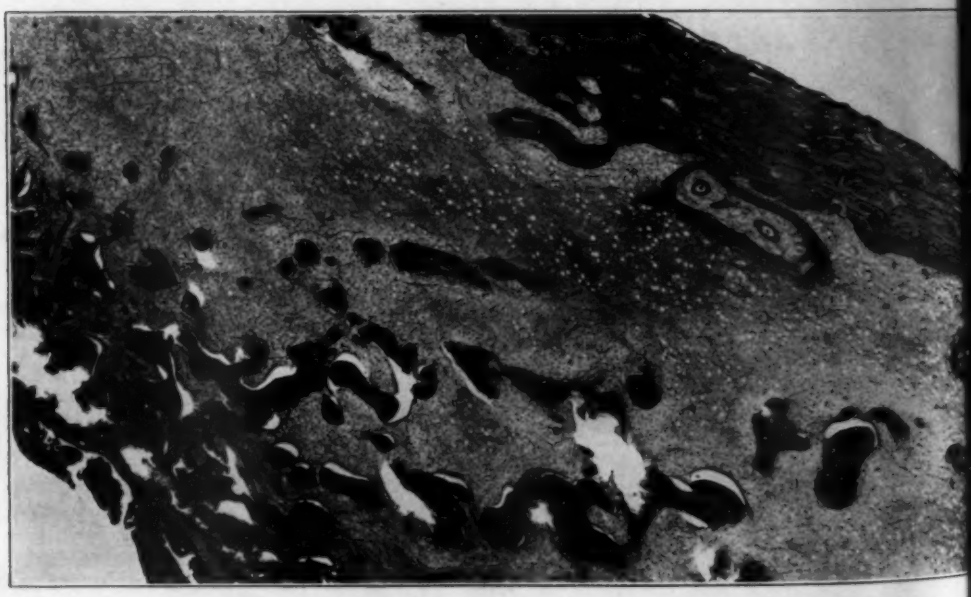

Fig. 8.—Replacement of the marrow tissues of the neck of the femur by sparsely cellular edematous fibrillar connective tissue (edema ex vacuo) twenty-seven days after division of the ligamentum teres and the nutrient vessel that pierces the cortex in the trochanteric notch. There is new bone formed about the blood vessels; × 15.

one third of the cortical bone was definitely delimited from the outer portion by its diminished staining reaction, empty lacunae and irregular eroded inner surface (fig. 7). At the limits of the infarcts of the shaft, except beneath an epiphyseal plate, there was considerable formation of spongy endosteal and periosteal new bone. The periosteal new bone was definitely delimited from the old cortical bone and was particularly abundant at the attachments of muscles and tendons. Occasionally, new

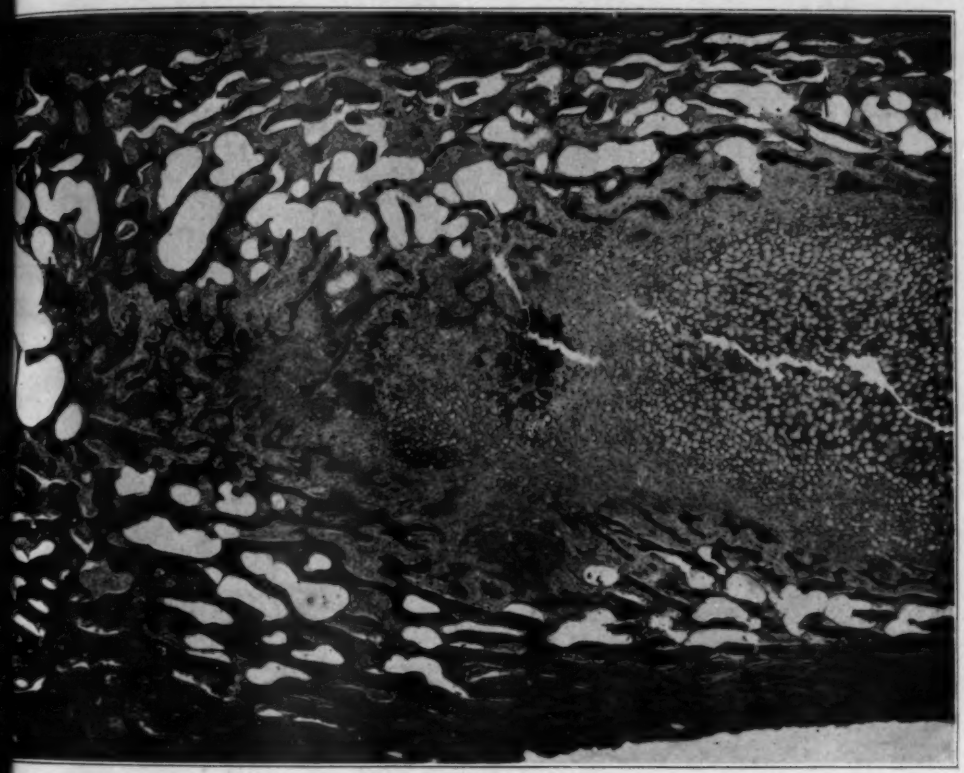

Fig. 9.—Distal end of an infarct of the shaft after forty-three days, demonstrating disseminated particles of carbon in the fibrous scar tissues, necrosis of the marrow tissues, eroded endosteum and proliferation of endosteal bone; × 15.

bone was formed about old spicules that had been caught in the zone of reaction. The center of the infarct at this time was anemic and composed of diminished, finely granular débris in which at times a relative increase in fat and many vessels occluded by carbon were noted. These were supported in a loose, fine, fibrillar network with clear, pale blue-staining spaces between the fibrils (edema ex vacuo), as shown in figure 8. In one young rabbit, examined fourteen days after infarction of the shaft by carbon, there were complete necrosis and liquefaction

of the distal epiphyseal cartilage line. This femur was considerably shorter than the control bone of the other leg. During this and later stages there were occasional large deposits of calcium salts at the distal epiphyseal line of the infarcts of the shaft and in the bony epiphysis. One such deposit was in the cortical bone of an infarcted region.

At the height of the reaction to an anemic infarct (fig. 9), which was from forty to fifty days after injection, the limiting walls were

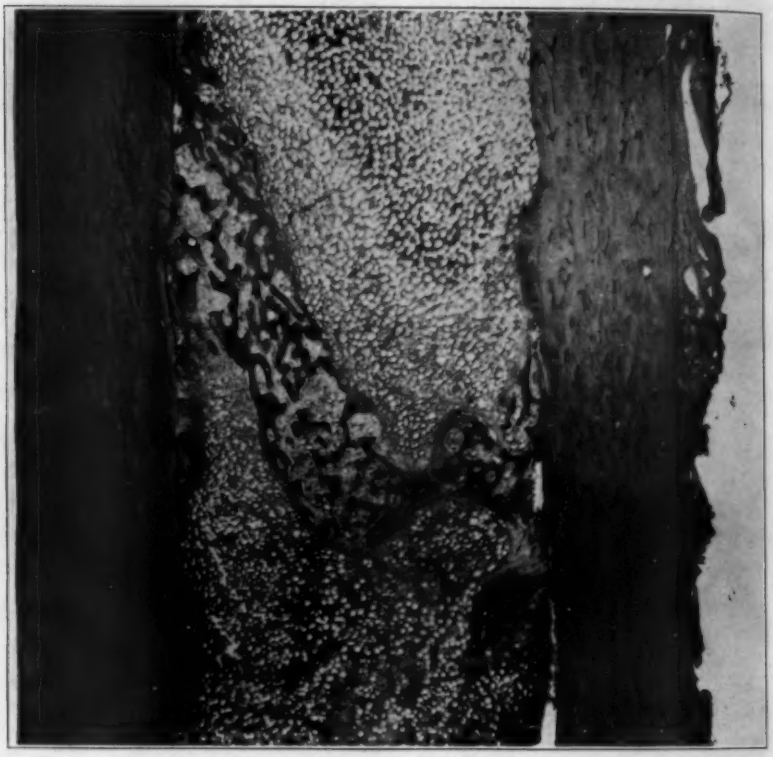

Fig. 10.—Septum of spongy bone through the medullary canal between necrotic and viable marrow tissues forty-three days after the injection of charcoal into the nutrient artery of the shaft of a femur. There is also formation of periosteal new bone; × 15.

dense fibroblastic tissue with many large multinucleated cells, and some bones had osseous bridges arching across the medullary canal-like septums (fig. 10). Around some of the newly formed blood vessels of this granulation tissue were collarets of cellular fibrous tissue and spicules of new bone. The original cortex was a narrow stratum of poorly stained, eroded bone between two layers of new osseous tissue formed from the endosteum and the periosteum (fig. 11). The new

bone associated with the periosteum was particularly abundant where its blood supply was enhanced by the attachment of a muscle or tendon; that developing along the endosteum was associated with an inner layer of fibrous tissue which maintained its blood supply from the ends of the infarct or by way of small periosteal vessels that had pierced the cortex (figs. 12 and 13). There was a marked diminution of cartilage in the epiphyseal lines as compared with the controls, and in some it was entirely absent.

Fig. 11.—Marked proliferation of endosteal and periosteal new bone of the cortex on one side of the shaft forty-nine days after infarction with carbon emboli. There is necrosis of the inner laminae of the bone on the opposite side without replacement by new bone. A branch of the nutrient artery to the shaft is occluded by carbon; × 15.

The ultimate fate of this reparative process was revascularization of the infarcted region, absorption of the débris and replacement of the dead cortical bone. Femurs examined three or four months after infarction by the usual procedure presented only the residue of necrosis and widely disseminated fine granules of carbon. In the medullary cavity were moderately edematous cellular tissues with many large multinucleated cells (foreign body giant cells) and blood vessels, some with

Fig. 12.—Cone-shaped fibrous tissue wall separating infarcted and viable tissues, with spicules of new bone extending from the endosteum forty-nine days after the injection of charcoal; × 11.

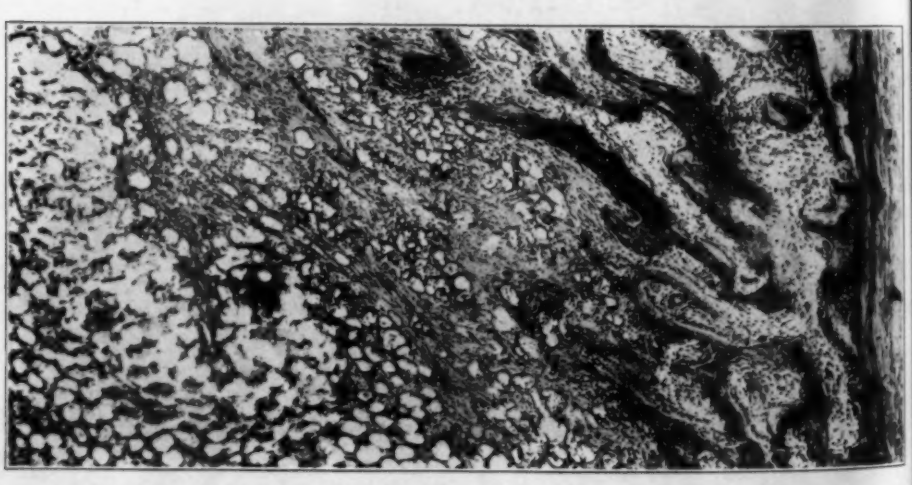

Fig. 13.—Higher magnification of proliferation of endosteal new bone in the limiting zone of reaction in figure 12; × 60.

collarets of dense fibrous tissue, in a connective tissue framework. A few small spicules of bone and masses of débris remained. At this time the original cortical bone, not yet displaced by new bone, was markedly eroded and quite distinct from the new.

Interference with the blood supply to different portions of the femur by the rupture of one or more nutrient vessels did not produce infarcts as described previously, and there was not the stimulus to promote reactionary changes. Ligation of the nutrient artery to the shaft decreased the staining reaction of medullary tissues in growing rabbits and produced slight necrosis in the metaphysis, which was of little consequence. An exception to this was the wedge-shaped metaphyseal infarct and overgrowth of epiphyseal cartilage line that occurred in a 3 week old rabbit. Division of the ligamentum teres in adult rabbits produced no change. In growing animals there was slight variable necrosis. When this procedure was combined with division of the vessel which centers the trochanteric fossa or with the injection of carbon into the nutrient artery to the shaft, the changes were marked. Interference with the vessel entering the notch alone produced only mild reactive changes localized to that portion of the proximal end of the femur.

COMMENT

The production of necrosis of bone by intra-arterial injection of particulate charcoal supports the belief that anemic infarction of these tissues may occur, despite their great vascularity. It also demonstrates that the vascular system of the rabbit's femur is closed, otherwise such emboli would be only foreign bodies disseminated in tissues without producing nutritional disturbance. While emboli such as these never occur in human tissues, it is fair to believe that fewer or smaller bodies acting similarly would cause proportionately less damage of the same general character. Consequently, particulate material within the vascular system of bone, by the very nature of its tissue structure, may be distributed to regions that normally have but one source of blood supply. If such particles are infectious and obstruct the circulation, a variably destructive agent is superimposed on a disturbance of nutrition.

The infarcts produced in rabbits were intimately associated with the metaphyses of growing bones. This is in accordance with the general view that the cartilage epiphyseal line is often the site of lesions of the bone considered as necroses. The difficulty encountered in producing infarcts in adult femurs and the tendency for these infarcts to be near the center of the shaft when the injection is made into the nutrient artery to the shaft emphasize the alteration in circulation that occurs when the epiphyses and the diaphysis unite. When the continuity of bone is interrupted, the severed portions can no longer depend on each other but must utilize other sources of blood supply. Should the col-

lateral circulation be inadequate, nutritional changes follow. This is the condition in so-called aseptic necrosis of the head of the femur, which occurs in adult as well as in growing femurs. In such conditions the continuity of bone is broken proximal to the entrance of epiphyseal vessels into the head from the periosteum and capsule, and the blood supply through the ligamentum teres is interrupted. Such a fragment is a segregated body, the fate of which depends on whether or not the tissues are revascularized and the necrotic bone replaced by new bone.

The bone tissues beneath articular cartilages are anatomically analogous to those situated beneath wide cartilage epiphyseal lines that are not penetrated by blood vessels. There is only a limited opportunity for the development of collateral circulation. It is reasonable to suppose that the many manifestations of subchondral necrosis may be primarily a nutritional disturbance associated with some other deleterious factor.

The infarcts produced experimentally in rabbits demonstrated absorptive reactive changes but no sequestration of dead bone. This is unlike many of the clinical entities embodying necrosis in which an impairment of circulation has occurred. Such differences may depend on the nature of the emboli or the trauma to which these regions of bone are subjected. By trauma in this sense is meant not severe sudden injury, but the trauma of friction, such as between component parts of a bone that are not equally capable of bearing a given stress. In other words, there is a break in the uniformly rigid character of the bone. Since weight bearing is the greatest stress placed on bones, such secondary changes probably would occur in bones of the legs and feet, particularly in the parts subjected to the maximum load. The added insult of weight trauma to such a focus may be sufficient not only to impair the healing but also to increase the lesion to the extent that a fragment of bone is entirely loosened from its bed, as in König's osteochondritis dissecans of the internal condyle of the femur (separating process of Axhausen). Compression fracture of bone trabeculae and their pulverization to bone detritus with hemorrhages often are present. There is no way of determining how frequently unrecognized focal necrosis of bone occurs, the so-called silent foci. An adequate reparative process is dependent probably on sufficient nourishment.

A disturbance in normal nutrition to an epiphyseal cartilage of a long bone interferes with growth. If there is diminished blood supply to a metaphysis, proliferation of cartilage may continue without ossification, while infarction of a cartilage plate produces necrosis. The endosteum and periosteum both react to a disturbance of nourishment to cortical bone by the production of new in the place of old bone. This proliferation of bone in the infarcts of the femurs was particularly active about the blood vessels at the junction of the viable and the necrotic

tissues. The deposition of inorganic calcium salts in infarcts of bone is probably calcification of nercotic tissues that already have a high content of this element.

SUMMARY

Infarcts were produced in the femur of young and adult rabbits by intra-arterial injection of a particulate suspension of charcoal and by interruption of one or more nutrient vessels outside the cortex of this bone.

The necrosis and reactive changes that occurred in from twenty hours to one hundred and fifty days after infarction have been described and correlated with a discussion of the more common clinical entities that concern necrosis in bone.

APPENDICITIS AND ACUTE INFLAMMATORY ABDOMINAL CONDITIONS IN SCARLET FEVER

REPORTS OF NINE CASES AND REVIEW OF THE LITERATURE

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This article deals with appendicitis and similar acute inflammatory abdominal conditions as they occur in scarlet fever. It was prompted by the fact that these conditions were seen repeatedly in patients with scarlet fever admitted to the Durand Hospital. The histories of these cases, a review of cases found in the literature available, and comments on the incidence, pathogenesis, morbid anatomic characters, clinical aspects and treatment are presented.

These abdominal disorders, principally of the right lower quadrant and particularly appendicitis, have been seen in the various exanthems, in anginal disorders and in disease of the respiratory tract and lungs. They have been observed in measles, mumps, whooping cough, chickenpox, smallpox and typhus.[1] During widespread disease of the upper respiratory tract and in pulmonary and influenzal conditions, appendicitis has been noted in almost epidemic proportions.[2] Appendicitis has followed inflammatory tonsillar disease [3] and rheumatic fever.[4]

From the Durand Hospital of the John McCormick Institute for Infectious Diseases, Chicago.

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(Footnotes continued on next page)

While there is no good reason for delimiting the occurrences to scarlet fever alone, it is the impression that they appear more frequently and in more unique situations in this exanthem. Certainly from a review of the cases in the Durand Hospital and of those in the literature it appears that the association of appendicitis and other inflammatory states with scarlet fever should be emphasized more than it has been.

Generalized, primary or idiopathic peritonitis in scarlet fever [5] is not included in the discussion.

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The following cases are reported from the Durand Hospital.

REPORT OF CASES

CASE 1.—H. N., a girl, aged 9 years, was admitted on April 22, 1913. On April 18 she had become suddenly ill with headache, malaise, chills, vomiting and a rash. Examination showed pallor about the lips, a tongue with large papillae, enlarged and reddened tonsils, enlargement of the lymph nodes in the neck, groin and axillae and a generalized scarlatiniform rash. The temperature ranged between 100 and 102 F. The white cell count was 10,000. On April 23 pain appeared in the right knee and wrists; it disappeared two days later. The temperature at that time varied between 100 and 101 F. Late on April 26 and through the following day pain in the right side of the abdomen and vomiting were present. The temperature ranged between 100.4 and 103 F. There were increased resistance and tenderness to palpation over McBurney's point. The white cell count was 31,000. Between April 27 and 29 the pain subsided. The temperature was normal on May 3.

CASE 2.—C. M., a boy, aged 15 years, was admitted on Aug. 25, 1913. He had been operated on for appendicitis at another hospital and was admitted because of a rash following operation. Examination revealed a brilliant scarlet rash over the abdomen and chest, enlargement of the lymph nodes of the neck, groin and pectoral region and a recent draining appendectomy wound. The temperature varied between 98 and 100.4 F. during the first five days and was normal thereafter. The white cell count was 10,000. Hemolytic streptococci were cultured from the throat. The rash faded about twenty-four hours after admission. At the end of five days the patient was returned to the first hospital. Details of the illness prior to the appendectomy and of the condition of the excised appendix were not obtained.

CASE 3.—D. P., a girl, aged 10 years, was admitted on May 11, 1914. She had had a diarrhea of one month's duration. On May 7, 8, 9 and 10 she suffered from dizziness, headaches, sore throat, increasing pain in the lower part of the abdomen, nausea and vomiting, fever and diarrhea. Examination disclosed an acutely ill child with a purulent nasal discharge, herpes of the lip, pallor about the lips, enlargement of the lymph nodes of the neck and a scarlet and punctate eruption. The abdomen was diffusely tender; the right lower quadrant was more tender and resistant to touch. There was a gonorrheal vaginitis. The white cell count was 16,000. Hemolytic streptococci were cultured from the throat. The temperature varied between 102 and 104 F. On May 12 the pain was definitely localized at McBurney's point and persisted so until May 14. On May 20 there was transitory pain in the ears.

CASE 4.—F. DeH., a woman, aged 21, was admitted on March 8, 1915. Four days previously she had become suddenly ill, with a loss of appetite, sore throat, constipation and a rash three days later. The temperature was elevated. On inspection, there were enlargement of the lymph nodes of the neck and of the papillae of the tongue, reddening of the pharynx, reddening and enlargement of the tonsils, pallor about the lips and a generalized and punctate red rash. The temperature averaged 98.5 F., with an occasional rise to 100 F. The white cell count was 8,100; in the differential smear there was a slight increase in eosinophils. On March 15 she complained of pain and tenderness in the right lower part of the abdomen. There was no muscular resistance. On March 16 the white cell count was 8,400. The pain disappeared on March 19.

CASE 5.—M. L., a nurse, aged 22, was admitted on May 28, 1917. Illness had developed suddenly on May 25. The patient complained of nausea and sore throat. A rash appeared on the day of admission. On examination the patient appeared

prostrated. Other signs were enlarged lymph nodes of the neck, a "raspberry tongue" and a confluent and red macular rash. On May 27 the white cell count was 16,000. The temperature varied irregularly from 99 to 101 F. and averaged 100 F. up to June 3. The rash and other symptoms and signs disappeared on June 4. There was profuse peeling of skin on June 6. Until June 21 the patient complained of nausea and pain in the right lower part of the abdomen. The abdomen was tender and resistant to pressure over McBurney's point. Successive white cell counts were 9,400, 10,600 and 12,300, with increasing numbers of polymorphonuclears. The temperature became normal. In consideration of the pain, tenderness and resistance of the abdomen and the increasing number of white blood cells appendectomy was considered, advised and refused.

CASE 6.—S. P., a girl, aged 5 years, was admitted on Nov. 24, 1917. In the past she had had "chronic appendicitis." On November 19 the appendix had been removed at another hospital. It was stated that the appendix was 9 inches (22.8 cm.) long, generally reddened at the distal 2 inches (5 cm.) and adherent to the mesentery. The temperature immediately following operation was 105. F. Cough was present on November 20 and a rash on November 22. Examination immediately after admission showed a moderately ill person. There were a "raspberry tongue" with ulcers, enlarged and reddened tonsils, a reddened pharynx, readily palpable lymph nodes of the neck and groin and a fine red macular rash with subcuticular flushing. The temperature varied between 99 and 100 F. On admission the white cell count was 11,900; on November 28 it was 18,200. The stitches sloughed out of the operative wound, and there was much foul-smelling pus. On December 6, the temperature ranged between 99.4 and 102 F. and the white cell count was 20,000. On December 8 there was a soft and boggy swelling behind the right ear; this gradually disappeared completely. The temperature was normal on December 9 and thereafter.

CASE 7.—R. M., a boy, aged 9 years, was admitted on July 24, 1919. His illness began on July 22 with itching, cutaneous eruption and vomiting. On examination the tongue was seen to be slightly reddened with accentuated papillae; the throat was reddened; the tonsils were reddened and enlarged, and the lymph nodes under the left side of the mandible were readily palpable. The rash had faded. The white cell count was 15,200. The temperature ranged between 99 and 100.4 F. The illness had the usual course until August 25, when the temperature rose to 100.8 F. and the patient complained of abdominal pain and vomited. There was no muscular resistance or tenderness. The condition lasted one day, and thereafter no untoward symptoms occurred.

CASE 8.—R. P., a boy, aged 15 years, was admitted on March 29, 1926. On March 27 the patient had been operated on for appendicitis at another hospital. The history prior to the operation had been that on the day before operation he complained of sore throat and vomited. There were no details regarding abdominal symptoms and signs. Two days after operation, a rash appeared on the body. A diagnosis of scarlet fever was made. Examination immediately after admission revealed pallor about the mouth, hyperemia of the throat and tonsils, coating of the tongue and accentuation of its papillae, moderate enlargement of the upper lymph nodes of the neck and a fading red-brown rash on the neck, axillae and abdomen. There was a recent appendectomy wound. The white cell count was 12,600. The temperature oscillated between 99 and 101.6 F. until May 4 when it was normal.

CASE 9 (personally observed).—O. E. W., a girl, aged 10 years, was admitted on Dec. 31, 1930. About two months prior to admission a moderately severe diabetes mellitus was discovered and had been treated adequately with an

TABLE 1.—*Cases in Which Appendicitis Was Definitely Proved by Operation or Postmortem Examination*

Case	Author, Reference	Sex, Age	General Clinical Features	Abdominal Signs and Symptoms	Observations at Operation or Postmortem Examination	Complication or Associated Disease
1	Stedman, C. E.: Boston M. & S. J. **95**: 756 (Dec. 26) 1876	M, 21	Dysphagia, chills, sore throat, rash on 2d day	Severe and colicky pains at umbilicus on 5th and 6th days; collapse and death	Appendix large, dilated and containtaining fecalith; perforation, surrounded by purulent peritonitis and adhesions	None
2	Chevassu: Arch. de méd. et pharm. mil. **28**: 36, 1896	M, 21	Diagnosis of scarlet fever, nothing unusual until 14th day	On 14th day abdominal pain, fever, vomiting, weak pulse and prostration; abdominal wall resistant; operation with excision of appendix; recovery	Operation: free pus, fibrinous adhesions about cecum; appendix inflamed and perforated	None
3	Julie, M. H.: Arch. de méd. et pharm. mil. **31**: 424 (June) 1898	M, ?	Diagnosis of scarlet fever, death 27 hours after onset	Vomiting; no details of abdominal pain	Intense hyperemia of abdominal viscera and volvulus of bowel; appendix long, folded on itself, containing pus and fecalith	None
4	Kelly, H. A., and Hurdon, E.: The Vermiform Appendix, Philadelphia, W. B. Saunders Company, 1905, p. 381	M, 8	Diagnosis of scarlet fever	Diagnosis of appendicitis in 3d week; excision of appendix; recovery	No details about appendix	Cervical lymphadenitis in 3d week
5	Veau, V.: Bull. Soc. de pédiat. de Paris **9**: 361 (Dec. 17) 1907	M, 12	Diagnosis of scarlet fever	On 3d day abdominal pain, fever and vomiting; appendectomy; recovery	Operation: appendix perforated, bound with adhesions and embedded in free pus	None
6	Veau, V., idid.....	M, 14	Diagnosis of scarlet fever	No details of abdominal distress; operation with excision of appendix; recovery	Operation: appendix enlarged and pelvic abscess	Polyarthritis
7	Veau, V., ibid.....	M, 8	Diagnosis of scarlet fever	No details; laparotomy with recovery	Abscess in right iliac fossa	Albuminuria and edema
8	David, cited by R. Kauffmann, Thèse de Paris, 1908 (see case reports of this author)	F, 6	Scarlet fever, gangrenous pharyngotonsillitis	Abdominal pain and muscular resistance in right lower quadrant; death	Appendix acutely inflamed and bound by adhesions	None
9	Routier, cited by Kauffmann...	M, 10	Diagnosis of scarlet fever	Appearance of abdominal pain 2½ weeks after onset; excision of appendix 8 weeks later	Meso-appendix inflamed; appendix obliterated and adherent to nearby bowel	None
10	Routier, ibid.	M, 17	Rash appeared 2 hours after diagnosis of appendicitis was made	Appendectomy on diagnosis of appendicitis; recovery	Appendix acutely inflamed and adherent to mesentery	None
11	Jalaguier, cited by Kauffmann	M, 15	Fever, vomiting and rash on 4th day after onset	Abdominal pain on 4th day with vomiting and elevated temperature, 7 weeks later appendectomy with recovery	Appendix ulcerated, embedded in adhesions and containing pus; meso-appendical lymph nodes enlarged	None
12	Guinan and Lefèvre, cited by Kauffmann	F. Inf.	Diagnosis of scarlet fever	Abdominal pain, vomiting and tenderness over McBurney's point; appendectomy with recovery	Acutely inflamed appendix with peritonitis	None
13	Rubsaet, cited by Kauffmann	F, 12½	Scarlet fever, death 3 days after onset	No details	Appendix hyperemic, edematous and covered with few adhesions	Pleurisy and bronchopneu-

13	Rubsaet, cited by Kauffmann	F, 12½	Scarlet fever, death 3 days after onset	No details	Appendix hyperemic, edematous and covered with few adhesions	Pleurisy and bronchopneumonia
14 to 18	Kauffmann, R: Thèse de Paris, 1908; Practitioner **82**: 289 (Feb.) 1909	3½ to 14; Av. 8	Diagnosis of scarlet fever; death on 2d to 9th day	Abdominal pain, elevated temperature, vomiting, resistance of abdominal wall; distention; collapse	Usually hyperemia of appendix and its mesentery and adjacent lymph nodes; occasionally acute necrosis of wall of appendix with contained pus; contiguous peritonitis	Cervical lymphadenitis, bronchopneumonia and pleurisy; diphtheria in one case
19-20	Kauffmann, R.	F, 4 F, 12	Diagnosis of scarlet fever; death	Definite diagnosis of acute appendicitis	Acute appendicitis; in one case, appendix was gangrenous and associated with general peritonitis	None
21	Kauffmann, R.: Ann. de méd. et chir. inf. **12**: 112, 1908	Child	Diagnosis of severe scarlet fever	Abdominal pain and vomiting on 2d and 3d days; death	Acute appendicitis with general peritonitis	None
22-23	Jores: Verhandl. d. deutsch. path. Gesellsch. **16**: 197, 1913	F, sisters	Epidemic of scarlet fever; death 2 days after onset	No details	Appendixes reddened and inflamed	None
24	Seitz, A.: Frankfurt. Ztschr. f. Path. pt 3, 470, 1913	F, 3	Diagnosis of scarlet fever; death on 5th day	No details	Appendix acutely inflamed and its wall thickened	None
25	Seitz, A., ibid.	F, sister of patient in case 24	Scarlet fever; death	No details	Appendix acutely inflamed and covered with fibrin	None
26	D. H. series,* case 2.....	M, 15	Diagnosis of appendicitis and operation; followed by rash; diagnosis of scarlet fever; hemolytic streptococci isolated from throat; leukocytosis; recovery	No details	No details	No details
27	D. H. series,* case 6.....	F, 6	Diagnosis of appendicitis, operation; rash on day following, with sore throat, cough and acute rise in temperature; hemolytic streptococci from throat; obvious scarlet fever; recovery	No details	Appendix 9 inches (22 cm.) long, reddened in distal 2 inches (5 cm.) and adherent to mesentery	Otitis ?
28	Canelli, A. F.: Riv. di clin. pediat. **17**: 362, 1919	Child, 2	Diagnosis of scarlet fever; death	No details	Acutely inflamed appendix	None
29	Newman, B.: M. J. & Rec. **119**: 80 (April 2) 1924	M, 6	Diagnosis of scarlet fever	Abdominal pain, fever and vomiting on 5th day; leukocytosis; appendectomy with recovery	Operation: acutely inflamed appendix	None
30	Thenebe, C. L.: Boston M. & S. J. **191**: 112 (July 17) 1924	M, 26	Sore throat, nausea and vomiting and rash in 24 hours	During convalescence, abdominal pain; elevated temperature and muscular spasm; operation and recovery	Operation: purulent appendicitis	None

TABLE 1.—*Cases in Which Appendicitis Was Definitely Proved by Operation or Postmortem Examination—Continued*

Case	Author, Reference	Sex, Age	General Clinical Features	Abdominal Signs and Symptoms	Observations at Operation or Postmortem Examination	Complication or Associated Disease
31	Thenebe, C. L., ibid.....	M, 17	Sore throat, nausea and rash	Abdominal pain and tenderness over McBurney's point; appendectomy and recovery	Operation: appendectomy, acute inflammation	None
32	Thenebe, C. L., ibid.....	F, 18	Sore throat, malaise and rash on 2d day	Abdominal pain and local tenderness; appendectomy with recovery 33 days later	Chronically inflamed appendix found at operation	None
33	Thenebe, C. L., ibid.....	M, 17	Sore throat, fever, malaise and rash	On 1st and 2d days pain in abdomen, localizing to right lower quadrant with tenderness; rash on 3d day; abdomen distended; on 4th day operation with recovery	Gangrenous appendix adherent to cecum; cecum edematous; fecal fistula as postoperative complication	None
34	D. H. series,* case 8.....	M, 15	Diagnosis of appendicitis; rash and sore throat noted; operation; vomiting; rash 2 days after operation; diagnosis of typical scarlet fever; fever, leukocytosis	No details	No details	None
35	Frank, H.: Deutsches Arch. f. klin Med. **164**: 150 (July) 1928	M, 11	Diagnosis of scarlet fever	On 4th day, abdominal pain and fever, on 5th, tenderness in upper part of abdomen, on 6th, distention of abdomen; laparotomy performed followed by death from general peritonitis	Operation: watery exudate in abdominal cavity, appendix 13 cm. long, retrocecal, tip touching liver; hemolytic streptococci from appendix and from peritoneal exudate after death	Otitis media
36	Bodenheimer, J. M., and Fleming, T. J.: New Orleans M. & S. J. **81**: 136 (Aug.) 1928	M, 16	Diagnosis of scarlet fever	Symptoms of appendicitis on 2d day; operation and recovery	At operation: acute appendicitis	None
37	Keisig, E.: Monatschr. f. Kinderh. **49**: 389, 1931	M, 7	Abdominal pain for 1 year preceding; diagnosis of scarlet fever	Abdominal pain, tenderness and resistance of right lower quadrant; operation immediately and 52 days later; recovery	First operation, pus in lower part of abdomen but no appendix seen; second operation, appendix perforated and containing a fecalith	
38	Finkelstein, quoted by Kaisig	?	Diagnosis of scarlet fever	Diagnosis of renal retention; laparotomy; death	Operation: perforated appendix situated behind bladder in abscess	Nephritis ?
39	D. H. series,* case 9.....	F, 10	Sore throat, fever and pain in chest at onset, pallor about lips, red throat, enlarged lymph nodes in neck, and rash; antitoxin given on admission, followed in 5 days by pain in chest, enlarged lymph nodes in pectoral region, urticaria, vomiting and abdominal pain, diabetic acidosis; receded; well until 10th day	On 10th day increasing abdominal pain, vomiting, tenderness and spasticity of abdominal wall; increasing leukocytosis; operation with removal of appendix; recovery	Operation: appendix generally hyperemic and enlarged; gangrenous at tip; pelvic abscess	Diabetes mellitus; serum sickness

adjusted diet and insulin. The patient became ill rather suddenly with a sore throat, fever and a vague pain in the chest. On examination, there were found a coated tongue with enlarged papillae, pallor about the lips, a red stippled palate, large and hyperemic tonsils, many shotlike lymph nodes in the upper triangles of the neck, a bright red and diffuse fine papular rash of the trunk and large and deep red lines in the creases of the elbows. The temperature varied between 98 and 100 F. The tests for reducing substance and ketone bodies in the urine were strongly positive. On a regulated diet of milk and cream and an increase in the dosage of insulin, the urine became normal. The white cell count was 19,500. Hemolytic streptococci were cultured from the throat. Three hundred thousand units of scarlet fever antitoxin was injected intramuscularly on admission. The temperature was normal from January 3 to January 5. The rash disappeared on January 4, and there was some peeling of skin on the chest and abdomen about the same time. On January 5 pain appeared in the left axilla with probably coincident enlargement of the lymph nodes of that region as well as of those along the pectoralis muscle on the same side and the upper triangles of the neck. The next day the temperature rose rapidly to 104.6 F., dropped to 99.6 F. on the day following and then rose again to 103.6 F. On January 5 and 6 there was severe, generalized and distressing urticaria. On the two following days headache, nausea and vomiting, abdominal pain and swelling of the eyelids appeared. The vomiting was so troublesome that all feeding by mouth was discontinued and resort made to retention and nutrient enemas. Reducing substance, ketone bodies, protein and casts were abundant in the urine. On January 9 the patient was comfortable and able to take food by mouth.

Late on January 10 and throughout the following two days the abdominal pain returned with rapid and increasing severity. There were much nausea and vomiting. The temperature averaged 99.6 F. On January 11 the abdominal wall was generally and exceedingly tender and resistant to palpation. The temperature rose in abrupt steps from 98 to 102.4 F. The distress was great enough to require morphine. On January 12 and 13 the white cell counts were 26,600 and 25,000, respectively.

Diagnoses of acute mesenteric lymphadenitis, pyelitis, pleuritis and pneumonia were considered. Because of the increasingly critical condition of the patient, a laparotomy was decided on. On January 13 Dr. E. M. Miller performed the operation. An appendix with an abscess at its tip was found. The appendix itself was markedly enlarged, generally hyperemic and gangrenous and perforated in its distal portion. Hemolytic streptococci were cultured from the wall and from the pus.

The first five days after operation were difficult and complicated by "gas pains." The temperature fluctuated between 98.6 and 102 F. The diabetic condition was readily managed. The patient recovered completely.

Attention is directed to a presentation of all the cases that could be found in the literature consulted. These are presented in tabular form and the various salient features of each case outlined. The cases are tabulated in three different groups: (1) those in which appendicitis was definitely proved by operation or postmortem examination; (2) those in which some abdominal organ other than the appendix was involved as proved by operation or postmortem examination; (3) those in which only the clinical aspects are known. In these it will never be definitely known whether the appendix or another organ was involved; therefore, such cases may be considered doubtful.

Each case is presented in numerical order according to the time of publication and analyzed according to:

Author
Age and sex
General clinical picture
Specific clinical picture of the abdominal disorder
Findings at operation or at postmortem examination
Presence of complications or of associated disease

The cases observed at the Durand Hospital are included for the sake of completeness.

TABLE 2.—*Cases in Which Some Abdominal Organ Other Than the Appendix Was Involved*

Case	Author, Reference	Age, Sex	General Clinical Features	Abdominal Signs and Symptoms	Observations at Operation or Postmortem Examination	Complication or Associated Disease
40	Nason, E. N., and Nason, W. S.: Brit. M. J. 1:908 (April 30) 1892	M, 7	Diagnosis of scarlet fever; several other members in family of patient died of malignant scarlet fever	Vomiting, abdominal pain and muscular resistance, death	Prominence and injection of Peyer's patches, enlargement of mesenteric lymph nodes	None
41	Rolly, F., in Mohr, L., and Staehlin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1925, vol. 1, p. 85	?	Diagnosis of scarlet fever	Death	Ruptured suppurating mesenteric lymph node and general peritonitis	None
42	Lewis, D.: personal communication to author	?	Diagnosis of scarlet fever	Abdominal pain, operation for appendicitis, recovery	Operation: lymph nodes between cecum and ileum inflamed, appendix normal	None
43	Lewis, D., ibid.	?	Scarlet fever	Abdominal pain, laparotomy, recovery	Operation: ileum diffusely inflamed for 3 feet (91 cm.), felt like "rubber hose"	None

In addition to the cases listed Gromski [6] reported two of abscess of the spleen, and Schlossmann and Meyer [7] stated that cholecystitis may occur.

The remainder of the article deals with comments on the incidence, pathogenesis, morbid anatomic changes and clinical and therapeutic aspects.

6. Gromski, M.: Two Cases of Splenic Abscess in the Course of Scarlet Fever, Przedglad pedyatryczny, 1912; abstr., Zentralbl. f. d. ges. inn. Med. u. d. Grenzgeb. **2**:695, 1912.

7. (*a*) Schlossmann, A., and Meyer, S.: Scharlach, in Pfaundler, M., and Schlossmann, A.: Handbuch der Kinderheilkunde, ed. 3, Leipzig, F. C. W. Vogel, 1923, vol. 2, p. 131. (*b*) Delage, J.: Bull. Soc. de pédiat. de Paris **30**:249 (April) 1932. (*c*) Saxl, O., and Gross, F.: Med. Klin. **28**:1168 (Aug.) 1932.

TABLE 3.—*Cases in Which the Exact Condition Was Not Ascertained*

Case	Author, Reference	Age, Sex	General Clinical Features	Abdominal Signs and Symptoms	Complication or Associated Disease
44	Sutton, A. M.: Lancet **2**: 1158 (Oct. 28) 1899	?	Angina and rash, diagnosis of scarlet fever	On 4th day, abdominal pain and vomiting, tumor felt in right lumbar region, recovery	None
45-49	Simonin: Bull. et mém. Soc. méd. d. hôp. de Paris **18**: 1388 (Dec. 27) 1901	M, 21 to 24	Diagnosis of scarlet fever	Abdominal pain, nausea and vomiting, tenderness over McBurney's point, spontaneous recovery, usually diagnosed "latent catarrhal appendicitis	Joint, muscular and possibly hepatic disorders
50-53	Bardon, C.: Quelques mots sur le rôle étiologique des maladies infectieuses dans l'appendicite, Thèse de Paris, Masson & Cie, 1914, p. 166	?	Usually severe anginа, jaundice	Tenderness deep in right lower abdominal quadrant on 3d to 17th day, usually diagnosed appendicitis, recovery	None
54	St. Paul, cited by Kauffmann, Thèse de Paris, 1908.	?, 2½	Diagnosis of scarlet fever	Abdominal pain, death	None
55	St. Paul, ibid.	?, 7½	Scarlet fever with marked intoxication	Abdominal pain, death (in foregoing 2 cases no postmortem examination)	None
56	St. Paul, ibid.	M, 11	Diagnosis of scarlet fever	Abdominal pain, recurred in 6 months	Nephritis
57	Marfan, cited by Kauffmann	M, 10	Diagnosis of scarlet fever	Abdominal pain	None
58-60	Kauffmann, R.	8½ to 11½	Diagnosis of scarlet fever	Abdominal pain and local tenderness 1 to 2 days after onset, recovery	None
61	Escherich and Schick, cited by Seitz (case 24)	F, 12	Diagnosis of scarlet fever	Early in disease, palpable tumor in right lower quadrant, tenderness over McBurney's point	None
62	Escherich and Schick, ibid.	?	Diagnosis of scarlet fever	Acute appendicitis during convalescence, no operation	None
63	Meyer, O.: Berl. klin. Wchnschr. **11**: 488, 1913	M, 4	Diagnosis of scarlet fever	Pain in abdomen and neck, vomiting, tenderness and muscular spasticity over McBurney's point, recovery, followed by 2 subsequent exacerbations	None
64	Meyer, O., ibid.	M, 11	Chill, fever, rash and swollen and hyperemic throat	On 2d and 3d days abdominal pain	Suppurative inguinal lymphadenitis
65	D. H. series,* case 1	F, 9	Headache, chills, vomiting, rash, hyperemic pharynx, enlargement of lymph nodes in neck, groin and axilla; fever and leukocytosis; recovery	On 4th day, abdominal pain with increased severity in lower right abdominal quadrant, vomiting and fever, tenderness over McBurney's point, much increased leukocytosis, regression on 6th day	Pain in right knee and wrists on 2d day, disappeared
66	D. H. series,* case 3	F, 10	Diarrhea for 1 month; headache, sore throat, rash and enlargement of lymph nodes; leukocytosis; hemolytic streptococci cultured from throat; recovery	Abdominal pain, nausea and vomiting near onset, tenderness in right lower quadrant, fever, pain definitely over McBurney's point on 2d day, gone by 4th day	Purulent rhinitis, gonorrheal vaginitis, otitis ?

* Durand Hospital series.

INCIDENCE

There is too little information at hand to permit any statement as to the frequency of occurrence of appendicitis and the other abdominal disorders in scarlet fever. A number of textbooks on infectious diseases, pediatrics, internal medicine and surgery do not mention the subject. Rolleston [8] stated that appendicitis may occur in scarlet fever but that he never saw a case. Heubner,[9] Jochmann [10] and Schlossmann and Meyer [7a] believe that it is not at all uncommon. Pospischill and Weiss [11] saw one patient with appendicitis in their clinical experience. Caiger [12]

TABLE 3.—*Cases in Which the Exact Condition Was Not Ascertained—Continued*

Case	Author, Reference	Age, Sex	General Clinical Features	Abdominal Signs and Symptoms	Complication or Associated Disease
67	D. H. series,* case 4	F, 21	Sore throat, malaise; rash on 3d day; lymph nodes of neck enlarged; slight eosinophilia; recovery	On 7th day, pain and tenderness in right lower quadrant, no leukocytosis, symptoms disappeared on 8th day	Nonspecific vaginitis
68	D. H. series,* case 5	F, 22	Sudden onset; sore throat, fever; rash on 3d day; enlargement of lymph nodes of neck; leukocytosis; recovery	On 24th day, pain in right lower quadrant with nausea and vomiting, tenderness in right lower quadrant, increasing leukocytosis, appendectomy recommended and refused	None
69	D. H. series,* case 7	M, 9	Eruption of skin, vomiting; pharynx hyperemic; lymph nodes about and under left ear enlarged; recovery	On 34th day, vomiting and abdominal pain for 1 day	None
70-72	Finklestein, quoted by Kaisig (case 37)	?	Diagnosis of scarlet fever	Diagnosis of appendicitis during course	None

* Durand Hospital series.

did not refer to any possible occurrence of these diseases in his report of one thousand and eight cases of scarlet fever. Table 4 may give some, but very likely poor, conception of the relative frequency.

8. Rolleston, J. D.: Acute Infectious Diseases, London, William Heinemann, Ltd., 1929, p. 274.

9. Heubner, O.: Lehrbuch der Kinderheilkunde, Leipzig, Johann Ambrosius Barth, 1906, vol. 1, p. 383.

10. Jochmann, G.: Lehrbuch der Infektionskrankheiten, Berlin, Julius Springer, 1924, p. 669.

11. Pospischill, D., and Weiss, F.: Ueber Scharlach (der Scharlacherkrankung, zweiter Teil), Berlin, S. Karger, 1911, p. 89.

12. Caiger, F. F.: An Analysis of 1,008 Cases of Scarlet Fever Admitted into the Southwestern Fever Hospital During the Year 1890, Lancet **1**:1249 and 1304 (June 6 and 13) 1891.

By further and more exhaustive studies it may be demonstrated that appendicitis and the other abdominal conditions occur much more often than indicated; I believe this to be true.

PATHOGENESIS

The pathogenesis of appendicitis and of the other conditions in scarlet fever is known only in general.

A common and much held view is that these conditions, at least appendicitis, are hematogenous metastatic products of which the hemolytic streptococcus, among others, is the cause and the pharynx the source of dissemination. No attempt will be made to dwell in any detail on this exceedingly controverted view, except to point out its numerous discussions as seen in the articles of Brenneman,[2d] Kaufmann,[13] Aschoff[14] and Christeller and Mayer.[15]

It is of interest to state the theory of Kretz,[16] who is a strong advocate of the hematogenous origin of appendicitis. According to him, the organism is conveyed by the blood stream to the lymphoid follicles and

TABLE 4.—*Frequency of Appendicitis in Scarlet Fever*

Source	Cases of Scarlet Fever	Cases of Appendicitis
Durand Hospital	4,863	0
Richardson, D. L. (personal communication)	4,823	8
Thenebe	250	4

their constituent capillaries. There the capillaries are destroyed, organisms liberated into the tissue spaces and variously acute exudative, proliferative and resolving inflammatory reactions incited. As an evidence of capillary damage emphasis is placed on the presence of submucosal hemorrhages. Aschoff denies any significance to these hemorrhages.

McMeans[17] gave an excellent review of the difficulties encountered in investigating the theory that appendicitis originates through the blood stream.

13. Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co. 1929, vol. 2, p. 835.

14. Aschoff, L.: Die Wurmfortsatzentzündung, Jena, Gustav Fischer, 1908, p. 85; Pathogenese und Aetiologie der Appendizitis, Ergebn. d. inn. Med. u. Kinderh. **9**:1, 1912; Zur Pathogenese und Aetiologie der Appendizitis, München. med. Wchnschr. **54**:1152 (June 4) 1907.

15. Christeller, E., and Mayer, E.: Appendizitis, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 4, p. 3, p. 469.

16. Kretz, R.: Angina und septische Infektion, Ztschr. f. Heilk. **27**:296, 1907; Studies upon the Etiology of Appendicitis, Internat. Clin. 1908, series 18, p. 285.

17. McMeans, J. W.: Experimental Appendicitis, Arch. Int. Med. **19**:709 (May) 1917.

Other theories may be briefly mentioned. Some believe that the organisms are swallowed and implanted in the interior of the organ affected. It has been suggested that there is a catarrh of the adjacent portion of the bowel which extends to the appendix. The fecalith may be important as a nidus of infection.

It is important to realize that the appendix is not invariably involved in the lesions which attract attention to the right lower quadrant of the abdomen. From the reports it may be seen that the ileocecal lymph nodes, probably the lymphoid tissue of the ileum, possibly mesenteric lymph nodes elsewhere and even the spleen may be involved in scarlet fever. Each of these may cause symptoms and signs so similar to those of appendicitis as to make a differential diagnosis difficult or impossible.

The whole lymphoid apparatus [18] is involved in the onset and course of scarlet fever. This may be inferred, for example, from the enlargement of the lymph nodes in the neck, groin and elsewhere as seen in routine examination. The reactions in these sites may regress or show further change in a small sphere, as, for example, in the neck. They may go on to more pronounced inflammation, to suppuration and to necrosis. The same reactions may exist in the appendix and other abdominal aggregates of lymphoid tissue so that the condition may occur in one of two ways: (1) as a part of the general reaction of the lymphoid apparatus at the onset and figuring in the production of abdominal symptoms of the prodrome of scarlet fever; (2) as one or several lymphoid aggregates that may go on to an acute abdominal lymphadenitis in the appendix, ileocecal mesentery and ileum and elsewhere.

MORBID ANATOMIC CHANGES

The abdominal organs that may be involved are: (1) the appendix (preponderantly); (2) the lymph nodes between the ileum and cecum with or without coincident appendictis; (3) the lymphoid patches of the ileum; (4) possibly the lymphoid tissue of the cecum itself; (5) the lymph nodes elsewhere in the mesentery, and (6) the spleen.

The "typhlitis" and "epityphlitis" of some authors, for example, Meyer,[19] may be examples of involvements listed under 2 to 5.

No unique changes are found in the involved appendix or other organs in scarlet fever.

The appendix may be simply enlarged, locally or diffusely reddened, kinked, displaced or intensely hyperemic, boggy, variably necrotic, ulcerated and perforated. The contents may be liquid or semisolid pus with an occasional fecalith. The surface may be covered with simple fibrin

18. Klemm, P.: Ueber die Erkrankung des lymphatischen Gewebes und ihr Verhältnis zur Appendizitis, Deutsche Ztschr. f. Chir. **81**:42 (March) 1906.

19. Meyer: Berl. klin. Wchnschr. **11**:488 (March 17) 1913.

to purulent exudate and be enmeshed in adhesions of various degrees of maturity. One, several or all the layers of the wall may become necrotic, leading to scarring and protection of the defect or perforation. The microscopic changes range from simple hyperemia and edema through various degrees of cellular infiltrations (polymorphonuclear, lymphoid and eosinophil) to necrosis of the layers with ulceration, hemorrhage and perforation.

R. Kauffmann (see cases 14 to 18 for reference) claims that the appendix is constantly involved in scarlet fever. According to him the vomiting seen at the onset is due to involvement of the appendix.

Occasionally the lymph nodes between the cecum and ileum are swollen and hyperemic. This reaction may be seen in connection with appendicitis but it often occurs alone.

CLINICAL ASPECTS

When one bears in mind that symptoms and signs referable to the right lower abdominal quadrant may arise from several organs, the outstanding rôle of the appendix must be emphasized. To indicate the great susceptibility of this organ to inflammations one may bear in mind Sahli's [3h] designation, the "abdominal tonsil."

Two situations in which these inflammatory conditions appear are important:

1. At the onset of scarlet fever the nausea, vomiting and sometimes the abdominal pain may be prominent enough to cause a diagnosis of appendicitis. This diagnosis may be readily possible when one fails to consider the possibility of a contact, the importance of a sore throat or infection of the upper respiratory tract, enlargements of lymph nodes in the neck, axillae and groins and beginnings of a rash in the axillae and groins and elsewhere. There may even be localized tenderness and muscular resistance. There may appear to be enough clinical evidence to justify operation. Soon after this a rash may rapidly develop and point to the true state of affairs. The appendix removed may actually be inflamed, thus bearing out the statement of R. Kauffmann as to the constancy of implication of the appendix. Cases 2, 6 and 8 of the Durand Hospital series indicate how readily one may operate for appendicitis in the face of oncoming scarlet fever.

Paget,[20] Trelat [21] and Martin [22] spoke of scarlet fever following appendectomy. They attributed the cause of the exanthem to the con-

20. Paget, J.: Scarlatina after Operations, Brit. M. J. **2**:237 (Aug. 27) 1864.

21. Trelat: De la scarlatine consécutive aux operations, Progrès med. **6**:721 (Sept. 14) 1878.

22. Martin, A.: Scarlatine traumatique dans une appendectomie, J. de méd. de Paris (series 2) **15**:425 (Oct. 18) 1903.

tamination of the operative wound with the appropriate organisms. The "surgical scarlet fever," so called by them, may well be that in which the prodromal symptoms mislead one to sole consideration of appendicitis instead of indications of scarlet fever setting in from the first.

2. The abdominal disorder may appear at any time after the onset of the illness and with or without any of the complications commonly associated with scarlet fever. This is seen in cases 1, 3, 4 and 7, in which the abdominal symptoms appeared as transitory events, by case 5, in which they were of considerable importance, and by case 9, in which operation was necessary.

Whenever abdominal symptoms and signs appear with any degree of persistence, appendicitis must be considered with all its implications of perforation and peritonitis.

Some of the clinical pictures that may appear are: The patient is scarcely over the preliminary symptoms and signs, convalescing or suffering from some common complication when he begins to complain of abdominal pain, usually with nausea and often with vomiting. The pain at first is usually diffuse, but it quickly centers in the right lower quadrant. The abdominal wall in that region may become tender and resistant to touch. The temperature, pulse rate or white cell count, or all three together, may be elevated. So far the attack may regress spontaneously and the diagnosis be in doubt. The attack may persist with intensification of all the symptoms and signs. Operation may be considered and performed. There may be hesitation, temporizing or poor observation and judgment of the course of the patient. Then the pain may become diffuse over the entire abdomen, the parietal wall generally tender and much resistant to palpation, the temperature septic, chills and sweats, the respirations faster and more shallow and the pulse rapid and weak. Obstipation, protracted vomiting, prostration and collapse may appear. Usually death occurs from generalized peritonitis secondary to perforation of the appendix, breakdown of the suppurating lymph node or ulceration and perforation of a lymphoid patch of the bowel.

The changes in temperature, pulse rate and white cells may be obscured by the presence of lymph node, middle ear and mastoid, pulmonary, pleuritic, joint, pericardial and other complications. In case 9 of this series the presence of diabetes and serum sickness made the diagnosis especially difficult.

It is of interest to direct attention to the fact that appendicitis may occur in several members of a family in a short time. This is thought by some to be due to a common sharing of some congenital defect. R. Kauffmann suggested that the several members were exposed to scarlet fever and made readily susceptible to appendicitis.

TREATMENT

When the presence of appendicitis is suspected the condition should be managed like the disease in general. One considers the qualitative, quantitative and chronological content and variations of the illness. The possibility of spontaneous regression under cautious and noninterfering observation is balanced against that of perforation and peritonitis. If the diagnosis is at all obscure, it is probably better on the whole to investigate with laparotomy. Even when the diagnosis of appendicitis appears certain, one may encounter merely ileocecal adenitis, an inflamed and stiffened ileum [23] or inflammation of a lymphoid mass elsewhere and a normal appendix. If such is the case, nothing further should be done. Lewis states that in all these cases operation should not be performed, but he emphasizes the great difficulty of an accurate diagnosis.

SUMMARY

About 73 cases of appendicitis and a small number of cases of other acute inflammatory conditions of the abdomen in scarlet fever were reviewed. Nine (of which 1 was personally observed by the author) are from the records of the Durand Hospital; the remainder are from the literature available and from communications.

The incidence appears to be small but is likely larger.

The disorders comprise inflammation of the appendix and of various mesenteric lymph nodes and masses of lymphoid tissue elsewhere in the abdomen. The relation of these conditions to involvement of the entire lymphoid system in scarlet fever has been indicated.

The pathogenesis is unknown, but the theory of infection through the blood stream spread and from the throat is plausible.

The anatomic changes do not appear to have any special features.

All these inflammations give nearly an identical picture which is principally that of pathologic involvement of the right lower abdominal quadrant. Two considerations are important: 1. The abdominal manifestations of scarlet fever at the onset may be sufficiently prominent to mislead one in the diagnosis of the oncoming exanthem. 2. When the symptoms and signs appear somewhere during the course of the fever appendicitis must be carefully considered.

The treatment is the same as that for appendicitis in general.

In the generally obscure background of the etiology of appendicitis as it may occur in any person or in several members in a family the presence of scarlet fever must be considered.

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23. Rockey, E. W.: Thickening of Terminal Ileum with Mesenteric Adenitis in Children, Northwest Med. **32**:145 (April) 1933. Lamson, O. F.: Mesenteric Lymphadenitis and Acute Appendicitis, S. Clin. North America **11**:1061 (Oct.) 1931.

SUBACUTE LYMPHOGRANULOMA INGUINALE

REPORTS OF TWO CASES

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The purpose of this paper is to emphasize the incidence of lymphogranuloma inguinale on the Pacific Coast. Especially a disease of tropical regions, where it has been abundantly described as climatic bubo, the disease has recently been reported from many European maritime cities and from ports of the Great Lakes.

In the confusion of names the disease should not be confounded with that termed "lymphogranulomatosis," a term often applied to Hodgkin's disease, or with those termed "ulcerative, pudendal disease" and "granuloma inguinale," presumably caused by protozoan infection.

Complete and easily accessible descriptions of the disease are contained in the articles by De Wolf and Van Cleve,[1] Sulzberger and Wise[2] and, especially from the standpoint of pathology, Lillie.[3]

Described briefly, the disease is a venereal infection caused by virus, showing a slight, transitory, mostly unobserved primary genital lesion of ulcerative or nodular type two or three weeks after exposure. This is followed by suppurative adenitis and periadenitis of the inguinal nodes. The livid and tender inguinal mass attains considerable size and softens and drains by a persistent sinus formation. Involvement of the deeper iliac chain occurs; in the later healing fibrotic process strictures of the rectum are apt to follow. These are especially common in women in whom primary infections in the cervix often result in the absence of the inguinal mass, the lymphadenitis affecting only the deep nodes. The course of the disease is from subacute to chronic, locally troublesome,

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From the Department of Surgery and Pathology, St. Luke's Hospital.

1. De Wolf, H. F., and Van Cleve, J. V.: Lymphogranuloma Inguinale, J. A. M. A. **99**:1065 (Sept. 24) 1932.

2. Sulzberger, M. B., and Wise, Fred: Lymphopathia Venereum, J. A. M. A. **99**:1407 (Oct. 22) 1932.

3. Lillie, R. D.: Inguinal Lymphadenitis with Special Reference to the Group Known as Climatic Bubo, Arch. Path. **8**:19 (July) 1929.

and with slight to moderate general symptoms of chills, fever, malaise and pain. Barring rectal stricture it is without serious sequelae.

The Frei test, a local reaction to an intradermal injection of 0.1 cc. of preserved pus in phenol from a known case of the disease, appears to be specific and persistent for years. The pathologic process in the involved glands is that of a tuberculoid reaction with, however, more remains of pus cells in the necrotic areas than are found in tuberculous caseation, with relatively few giant cells and often with hemorrhage or deposit of hemosiderin from an old hemorrhage. Epithelioid cells are variable in abundance, and pronounced fibrosis marks the later stages of the disease. Obliterative endarteritis is absent or less marked than in a syphilitic lesion. Barring secondary infection, bacteria are not found in smears or cultures as they are in chancroidal bubo, in the bubo of bubonic plague and in pyogenic lymphadenitis. The virus appears to be transmissible to mice and to monkeys,[4] at least. Transmissibility to other animals is yet uncertain.

REPORT OF CASES

The following reports illustrate the main features of the disease:

CASE 1.—J. B. K., aged 43, white, a sea captain, consulted one of us (A. W.) on July 7, 1932, with regard to a lump in the left inguinal region of three weeks' duration. His familial and personal history were irrelevant, except that during the last three and a half years he had been sailing to and from the Orient and had had a certain amount of time ashore in the East.

His present illness began three days out from Hong Kong with the development of headache, chilliness, pain in the lower part of the back, some coughing and profuse perspiration. He thought that he had a fever also. These symptoms gradually subsided with the exception of the headache and backache, which persisted almost to the time he came for consultation. Four days after the onset of these symptoms, he noticed a lump in the left inguinal region which was slightly sore and which had gradually become more painful and larger since it was first noticed. During the preceding two weeks he had lost about 10 pounds (4.5 Kg.).

The patient was a self-contained person who did not pay much attention to his symptoms. A general physical examination showed no abnormal condition with the exception of that in the left groin. Here was a mass 3 by 2 inches (about 7 by 5 cm.), slightly reddened, with three or four dark pigmented spots ½ inch (about 1 cm.) in diameter. The dark areas were fluctuant, and the skin appeared to be attached to the underlying mass. Over the remainder of the swelling the skin appeared to be reasonably movable. The mass was definitely superficial to the inguinal fascia, and the finger could be inserted into the external inguinal ring and felt to be definitely beneath this mass. The patient's temperature was 102 F., and he looked much sicker than would be expected from an inflammation of this size. A blood count showed: red blood cells, 4,730,000, and white blood cells, 19,000, with polymorphonuclears 80 per cent. The hemoglobin concentration was

4. Levaditi, C.; Ravaut, P.; Lepine, P., and Schoen, R.: Etude etiologique et pathogénique de la maladie de Nicolas et Favre, Ann. Inst. Pasteur **48**:27 (Jan.) 1932.

80 per cent. The urine contained albumin, a trace of acetone, occasional hyaline casts, white blood cells and numerous mucous threads.

The patient was admitted to St. Luke's Hospital that afternoon, and a small amount of pus was aspirated from the inguinal region on two occasions. The specimens showed pus cells and fibrin but no bacteria. A culture was negative. Injections into guinea-pigs also gave negative results, and the blood cultures remained negative.

During the first two weeks in the hospital his temperature continued to fluctuate between 102.2 F. and normal, gradually subsiding to normal. Treatment included the application of hot compresses and irradiation with ultraviolet rays from an air-cooled, quartz mercury vapor arc lamp, alpine light but no antimony compounds. One area in the groin broke down completely under treatment. The entire mass of glands in the left groin was then excised under general anesthesia. The glands lay entirely superficial to the external oblique fascia and were adherent in many places to the overlying skin. The skin was removed with the glands in a single block of tissue. The glands extended from just above the inguinal ligament to the saphenous opening. The wound was left wide open, and packed with gauze saturated with potassium permanganate.

The pathologic report on this tissue (W. P. S.) was as follows: Paraffin sections from the inguinal node showed a loss of lymphoid tissue and diffuse fibrosis in some fields and areas of caseation in others. Foreign body giant cells were present in small numbers. Endothelial proliferation of Hodgkin's type and epithelioid cells of the tubercle type were not found. While caseation, giant cells, round cells and fibrosis were all present, in no place were they arranged in typical tubercle formation. This histologic condition was consistent with lymphogranuloma inguinale (tropical bubo), with the possibility of atypical tuberculosis.

In a few days the pack was removed, and the wound was treated with equal parts of castor oil and balsam of Peru.

The patient made an uneventful recovery following the excision of the glands, and was discharged from the hospital seventeen days later with the wound almost entirely healed.

Case 2.—J. W., aged 42, white, a radio engineer, consulted one of us (B. C. N. O'R.) on Feb. 21, 1932, stating that in the previous April or May he was standing astride a heavy machine cover and attempted to lift it. His left foot slipped, and he felt a sudden severe pain in his left groin. He examined the area, but found no unusual lumps or signs, and in half an hour the pain disappeared. Three or four days later, on examining this same region, he found a painful area which he thought was due to irritation by his clothing. He suspected that he had a rupture and consulted a doctor, who told him that he had not, but said that he had an enlarged inguinal gland, attributable to a small pustule on his buttock. In about ten days the lump in the groin disappeared.

On Feb. 7, 1933, he noticed the lump again, and at this time had chills and slight fever for about a week. He made several attempts through the Industrial Accident Commission to have his disability connected with his original strain, all of which were unsuccessful. On further questioning we found that in 1926 he had been employed on a vessel calling at various ports in the Bay of Bengal, and that he had had swollen glands in the left groin for about two weeks. He stated that he used hot compresses and the swelling "came to a head and pus ran out and then healed." In 1927 the shipping company employing him wished to send him to a hospital in England for a diagnosis, but the patient refused this since the swelling in the groin had disappeared.

Examination showed the general physical condition to be normal, with the exception of the left groin, in which there were enlarged, fluctuating glands. The skin over them was dusky and adherent. There was little redness or other evidence of inflammation. The glands were tender. Exposure to venereal diseases was denied. The blood showed: a hemoglobin concentration of 90 per cent; red blood cells, 4,710,000 per cubic millimeter; color index, 0.96; white blood cells, 10,640 per cubic millimeter, with polymorphonuclears, 67; small lymphocytes, 18; large lymphocytes, 6, and transitionals, 7 per cent. The Wassermann, Kolmer and Kahn reactions were negative. The deep iliac nodes were distinctly enlarged and palpable.

The patient was admitted to St. Luke's Hosiptal with a diagnosis of lymphogranuloma inguinale, and was tested with Frei's antigen, which had been furnished the hospital by Dr. H. F. de Wolf of Cleveland. The results of the intradermal tests showed, first, an itching and burning, with a 9 cm. area of erythema appearing fifteen minutes after the injection and fading in thirty minutes, and second, at seventy-two hours a 5 cm. wheal with a central papule.

The patient refused to allow surgical intervention at that time, but returned three weeks later for operation. The operative procedure was as follows: The inguinal incision was made around a mass of inguinal glands in the groin. These were easily freed from the external oblique fascia, which was exposed and left bare. Some glands, down at the external inguinal ring, were included in the resected tissue, and two or three were excised from the saphenous opening. The femoral vessels were seen, but were not injured. There were two discolored areas of skin which were attached to the underlying necrotic gland tissue. The upper area was included in the resected mass by extending the incision to surround it, making the incision elliptical. The lower area of the two was below the fold of the groin, and because by inclusion of this area the scar would be drawn crossing the inguinal fold it was not removed, but the glands were scraped away from underneath so that only the skin was left.

The pathologic report (W. P. S.) was as follows: There was a mass of gland and periglandular tissue from the groin, consisting of fatty and fibrous tissue and two broken-down glands, the larger about 2 cm. across, partly fibrous and with multiple foci of soft, creamy, caseous-looking material, each about 1 mm. across. Cultures of this material were sterile after ten days' incubation. Smears were negative for acid-fast bacilli. Sections showed the lymphoid tissue markedly reduced by replacement by a formation resembling a tuberculoid granuloma. In many fields there was diffuse, dense, almost hyaline, fibrosis. In others the granulomatous foci took the form of caseous centers surrounded by a few epithelioid cells; outside of this was a sharp zone of fibrosis that quite rapidly became dense in the outer layers. Round cells were represented only by the remains of the lymph node cells, and giant cells of the foreign body type were found only on careful and prolonged search. The adjacent vessels showed thickening and arteritis, but without perivascular round cells.

The various treatments advocated for this disease include tuberculin injections, injection of glycerin into the glands and sinuses, roentgen ray and ultraviolet ray therapy, intravenous injections of 1 per cent solutions of antimony and potassium tartrate and surgical resection. In the cases of rectal stricture, surgically inaccessible, the treatment with antimony certainly should be used. The two cases reported here responded rapidly and perfectly to surgical excision. That such excision is the

method of choice is borne out by the experience of one of us (A. W.). While surgeon at the old Marine Hospital in San Francisco years ago, he saw many sailors with this condition, presenting in the groin dirty, ulcerating, sloughing wounds that had been present for months, and had been treated elsewhere by incision. The wounds were often necrotic and so foul that the man had the sinus packed with oakum to kill the stench. Nevertheless, even these lesions, months old, healed with rapidity following radical excision.

II. USE OF BACTERIOPHAGES IN TREATMENT OF COLON BACILLUS INFECTIONS OF THE URINARY TRACT

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In offering a brief summary of our experience in the application of bacteriophage therapy to urinary infections with colon bacilli, we are well aware of earlier observations in this field. A review of the earlier work seems superfluous, but we wish to acknowledge our indebtedness to the pioneer studies, and their aid as a guide in our own attempts. Those who have worked in this field have, as a rule, observed some favorable effect, apparently due to the bacteriophage in some instances, and an occasional strikingly favorable result evidently related to the use of this agent. However, there have been many disappointments and unexplained failures, so that some of the workers with extensive experience have lost their early enthusiasm for the use of bacteriophages in this field.

We are inclined to think that some of the failures may have been due to lack of understanding of the limitations of bacteriophage action and to lack of sufficiently intimate and sympathetic cooperation between the clinician and the bacteriologist. From experience in our own series of cases we are convinced that the technic of application of the remedial agent may sometimes determine the issue between success and failure. This point is particularly well illustrated by the work of Dr. George C. Leckie [1] at the Newark City Hospital. This urologist, employing bacteriophages supplied by our laboratory, treated 14 patients with colon bacillus infections of the urinary tract, with 7 recoveries with bacteria-free urine, 6 instances of marked symptomatic improvement with persisting bacilluria and 1 failure.

These studies have been aided by a grant from the Josiah Macy Jr. Foundation.

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1. The patients of Dr. Leckie are included in our summarized figures. We understand that he will present his detailed observations in a paper of his own.

We have more or less satisfactory records for 388 patients from whom specimens of urine were sent to us for bacteriophage service. In 118 of these specimens the laboratory study revealed no evidence of infection. In 270 bacterial infection was recognized. In these 270 specimens our records indicate the presence of 318 infectious organisms, some of the samples containing 2 or even 3 or 4 different organisms. Table 1 indicates the proportion in which the various types of microbes were found and also gives an analysis of their relative susceptibility. The predominance of Escherichia acidi-lactici is noteworthy. The members of the Escherichia group maintained almost the same frequency of resistant strains, but the Aerobacter group was almost entirely resistant to the bacteriophages in our collection.

TABLE 1.—*Susceptibility to Phages of Organisms in Urinary Infections*

		Resistant		Partial Lysis		Susceptible	
Organism	Total Strains	Number	Per Cent	Number	Per Cent	Number	Per Cent
Escherichia acidi-lactici	115	13	12	24	21	78	67
Escherichia communior	34	6	18	6	18	22	64
Escherichia coli	15	2	13	6	40	7	47
Aerobacter group	44	43	98	1	2	0	0
Miscellaneous bacilli*	55	32	58	9	17	14	25
Staphylococcus aureus	11	2	18	0	0	9	82
Staphylococcus albus	16	11	68	1	7	4	25
Streptococcus haemolyticus	9	9	100	0	0	0	0
Streptococcus (indifferent)	7	7	100	0	0	0	0
Streptococcus viridans	3	3	100	0	0	0	0
Streptococcus with partial hemolysis	9	9	100	0	0	0	0
Totals	318	137		47		134	

* This group consists of atypical Escherichia, 35; Alcaligenes faecalis, 3; proteus group, 10; Shigella paradysenteriae (Flexner), 1, and Pseudomonas aeruginosa, 6.

Of the 270 patients with urologic conditions with positive cultures there were 72 in whose specimens of urine organisms of the colon bacillus group were not found and 198 in whose specimens colon bacilli were present. For various reasons bacteriophage therapy was not used for 101 of these patients. The chief reason was our failure to find an effective bacteriophage. However, in 18 instances in which an effective bacteriophage was successfully prepared in the laboratory it was not used in treatment. To 97 patients treatment with bacteriophage was given. For 24 of these we lack adequate information in regard to the result; for 23 there was a report of failure; 27 showed symptomatic improvement without final bacteriologic proof of eradication of the infection, usually because no specimen of urine was submitted, and for 23 there was clinical success coupled with bacteriologic proof of bacteria-free urine. These data are shown in table 2.

A few patients will be considered in some detail in order to illustrate the methods employed and the experiences in success and failure.

REPORT OF CASES

CASE 1.—C. C., a white woman, aged 43, was admitted to the hospital on Sept. 11, 1929, complaining of pain in the lower part of the abdomen, menorrhagia and urinary frequency. On September 12, the appendix, uterus, tubes and ovaries, except a portion of the left ovary, were removed by Dr. John F. Erdmann. There were multiple fibroids in the uterus and evidence of chronic inflammatory disease of the other organs removed. During the third night after the operation urinary frequency became evident, and the patient complained of irritation in the bladder. The urine specimen passed at 6 a. m. on September 17 contained an excessive number of leukocytes, and on that day and the next methenamine was given. The irritation of the bladder continued. On September 20 the sutures were removed from the abdominal wound, and the patient sat up in a chair for half an hour. Her temperature rose, and she became nauseated, and the urine passed on September 23 contained many pus cells. A specimen of urine obtained by catheterization on the morning of September 24 yielded over 500,000 colonies of colon bacilli per cubic centimeter. When the result of the culture became known, the administration

TABLE 2.—*Patients with Urologic Conditions Classified According to Bacteriologic Diagnosis and Relation to Bacteriophage Therapy*

Total patients		388
Patients with negative cultures		118
Patients with other than colon bacillus infections		72
Patients with colon bacillus infections		198
Bacteriophage not used in treatment	101	
No effective bacteriophage found	57	
Effective bacteriophage prepared	18	
Partially effective bacteriophage prepared	23	
Request withdrawn	3	
Bacteriophage used in treatment	97	
Result not adequately reported	24	
Failure of bacteriophage therapy	23	
Symptomatic improvement	27	
Success with bacteriologic proof	23	

of methenamine was again started and continued until September 28. Disodium monohydrogen phosphate was also given on September 26, 27 and 28. On September 28 the patient had her worst day, with persistent vomiting, a frank chill and a rise of temperature to 105 F. A blood culture taken on this day was negative. The disodium monohydrogen phosphate and methenamine were discontinued, and potassium citrate in 15 grain doses was given in order to get the urine nearly neutral in reaction, in preparation for bacteriophage therapy. The fluid intake was kept at a high level.

Meanwhile the colon bacillus from the urine of September 24 had been found susceptible to bacteriophage, and a bacteriophage specific for this organism had been prepared in broth. A subcutaneous injection of 1 cc. of this broth filtrate was given at 8 p. m. on September 30. At 1:40 p. m. on October 1, a specimen of urine was obtained by catheterization, and 10 cc. of bacteriophage filtrate diluted with 90 cc. of saline solution was introduced into the urinary bladder. The catheterized urine obtained at this time was studied in the bacteriologic laboratory. It was alkaline (p_H 7.3), and its cultures yielded more than 500,000 colonies of colon bacilli per cubic centimeter. Serial filtrations of cultures failed to reveal the presence of bacteriophage in the urine. At 6:30 p. m. on this day a second subcutaneous injection of bacteriophage broth was given, this time a dose of 2 cc. On October 2 chemical analysis of the blood showed the urea nitrogen to be 6.9

mg. per hundred cubic centimeters, a low figure. At 2 p. m. on this day urine was again obtained by catheterization, and 10 cc. of bacteriophage diluted with saline solution was again introduced into the bladder. This urine specimen was neutral in reaction (p_H 7), and the plate cultures showed a marked diminution in the number of colonies, there being approximately 125,000 per cubic centimeter. Furthermore the filtrate of this urine exhibited a strong bacteriophage action on cultures of the infecting bacterial strain. Administration of bacteriophage was discontinued. After October 2 the fresh urine specimens, as passed, were frequently tested with litmus paper by the nurse. On October 3 and 4 these tests showed an acid reaction. On October 5, the reaction became neutral and then alkaline, returning to acid on the morning of October 6 and changing to neutral in the afternoon and to acid again on the morning of October 7. On October 8 the morning urine, tested by comparator, showed a p_H of 6.8. The dosage of potassium citrate was increased to 60 grains (3.6 Gm.) for this day and 75 grains (4.5 Gm.) for October 9. The morning urine of October 10 was distinctly alkaline (p_H 7.4). Bacterio-

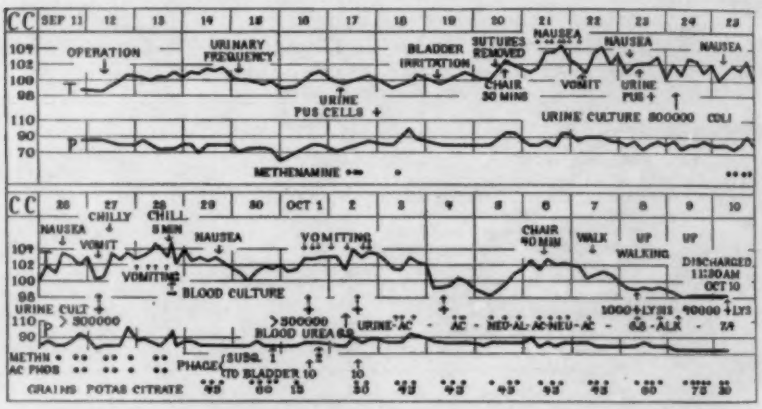

Chart 1 (case 1).—Abridged clinical chart for C. C., showing the course of the temperature (T) and pulse rate (P) together with outstanding features of the clinical record.

logic study of the morning urine of October 4 revealed many swollen and distorted bacilli in the microscopic preparation. The cultures revealed a further diminution in viable bacteria, there being less than 100,000 colonies per cubic centimeter of urine. The urine filtrate contained a strongly active bacteriophage. The morning urine of October 8 yielded only about 1,000 colonies per cubic centimeter of urine, and these colonies showed the peculiar effects of bacteriophage as they grew on the plates. The broth cultures failed to show any colon bacilli, presenting only contaminating cocci and diphtheroid bacilli. The filtrate revealed the presence of a strongly active bacteriophage. The last urine specimen, obtained on October 10, was almost clear. Its reaction was alkaline (p_H 7.4). The sediment contained pus cells and irregularly stained swollen and distorted bacilli. Plate cultures yielded 40,000 colonies per cubic centimeter of urine. The filtrate of the urine still contained active bacteriophage, but in diminished concentration as compared with the urine of October 8. The lytic agent had, however, persisted in the urinary tract for eight days.

The patient improved clinically from the time the methenamine and disodium monohydrogen phosphate were discontinued on September 28. She was rather miserable on October 1 and 2 and resented somewhat the administration of the bacteriophage. After October 7 she was comfortable, and when discharged on October 10 she was free from symptoms. She has remained well. Our requests for further specimens of urine have not been granted. This patient's condition was classified as acute postoperative pyelitis clinically improved but without bacteriologic proof of success.

Case 2.—A. R. H., a white woman, aged 31, was admitted to the hospital on Feb. 25, 1930. On this day the appendix was removed, and a constricting band which obstructed the small intestine was released. Following the operation the patient was catheterized at 6 p. m. on the same day and also twice on the following

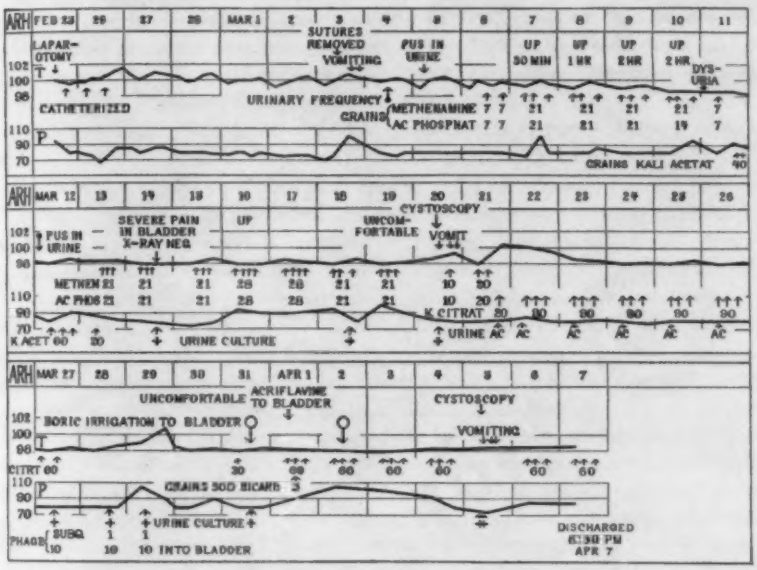
ARH
FEB 23 24 27 28 MAR 1 2 3 4 5 6 7 8 9 10 11
LAPAROTOMY
SUTURES REMOVED
VOMITING
PUS IN URINE
UP 30 MIN
UP 1 HR
UP 2 HR
UP 2 HR
DYSURIA
CATHETERIZED
URINARY FREQUENCY
GRAINS
METHENAMINE 7 7 21 21 21 21 7
AC PHOSPHAT 7 7 21 21 21 19 7
GRAINS KALI ACETAT 40
MAR 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
PUS IN URINE
SEVERE PAIN IN BLADDER
X-RAY NEG
UP
CYSTOSCOPY
UNCOMFORTABLE
VOMIT
METHEN 21 21 21 28 28 21 21 10 20
AC PHOS 21 21 21 28 28 21 21 10 20
K CITRAT 20 90 90 90 90 90 90
K ACET 60 20
URINE CULTURE
URINE AC AC AC AC AC AC
MAR 27 28 29 30 31 APR 1 2 3 4 5 6 7
UNCOMFORTABLE
ACRIFLAVINE TO BLADDER
CYSTOSCOPY
BORIC IRRIGATION TO BLADDER
VOMITING
CITRT 60 30 60 60 60 60 60
GRAINS 300 BICARB 3
SUBQ 1 1
PHAGE 10 10 10 INTO BLADDER
URINE CULTURE
DISCHARGED 6:30 PM APR 7

Chart 2.—Abridged clinical chart for A. R. H.

day. The postoperative progress was satisfactory until March 3, when the sutures were removed. Following this there were severe abdominal pain and vomiting at 9:15 and again at 11:15 p. m. On the next day there was a constant desire to void urine, and a foul odor of the urine was noted by the nurse. Clumps of leukocytes were recognized by microscopic examination of the urine on March 5. Methenamine and disodium monohydrogen phosphate were given, beginning on March 6, and the patient was allowed to be out of bed each day from March 7 to 10. Marked dysuria was noted during the night of March 10, and on March 11 the methenamine and phosphate were discontinued and potassium acetate was given. On March 12, clumps of pus cells were found in the urine, as before. Methenamine and acid phosphate were started again on March 13. On March 14 the discomfort in the bladder was severe, and after consultation urine was sent to the laboratory for culture and microscopic examination for tubercle bacilli. Roentgenologic examination of the kidneys on this day gave negative results. The

urine was negative for tubercle bacilli. It contained pus cells and gram-negative bacilli, which on culture proved to be colon bacilli of the lactic acid variety.

The methenamine and disodium monohydrogen phosphate were continued until March 21. Meanwhile a culture of the bladder urine on March 18 confirmed the previous findings. The colonies of colon bacilli on the most dilute plate culture inoculated with 0.05 cc. of urine were too numerous to be counted. There was increasing discomfort on March 19. On March 20 a cystoscopy was done with the patient under nitrogen monoxide-oxygen anesthesia. Opaque catheters were passed into both ureters, and roentgenograms made. These gave essentially negative results. At this time specimens of urine were collected from the bladder and from each ureter. Bacteriologic study of these specimens showed approximately 10,000,000 viable colon bacilli per cubic centimeter in the bladder urine, but both the ureteral specimens were found negative on microscopic and cultural examination.

Following the cystoscopy, the patient vomited three times, and her temperature rose to 100.4 F. on March 21. The methenamine and disodium monohydrogen phosphate were discontinued on this day and administration of potassium citrate was begun. The dose of the citrate was increased to 90 grains (5.4 Gm.) daily, but the urine remained persistently acid in reaction. Meanwhile the culture of colon bacilli had been tested against ten different races of bacteriophage in the laboratory, and the activity of two of these had been enhanced by six serial filtrations. Preparations in broth were made available for therapeutic use. On March 27, at 11 a. m., bladder urine was obtained by catheter, and 10 cc. of the bacteriophage broth diluted with 90 cc. of sterile saline solution was left in the bladder. Apparently through some misunderstanding, the citrate was discontinued at this time. Cultures of this bladder urine of March 27 yielded 100,000 colonies per cubic centimeter, and the organism was tested and found susceptible to the bacteriophage used in therapy. On March 28, at 4 p. m., the bladder was again catheterized and 10 cc. of the bacteriophage broth in 90 cc. of saline solution was left in the bladder. A subcutaneous injection of 1 cc. of the bacteriophage broth was given at this time. This procedure was repeated at 10 a. m. on March 29. A moderate rise in temperature was apparently caused by the subcutaneous injections. Bacteriologic study of the urine specimens of March 28 revealed no pus cells and no recognizable bacteria on microscopic study, but the cultures yielded 20,000 colonies per cubic centimeter of urine. These bacteria were found by test tube experiment to be susceptible to the phage used in therapy. The catheterized specimen of March 29 revealed cellular débris and bacilli on microscopic study, and the cultures yielded more than 10,000,000 colonies per cubic centimeter of urine. This organism was now found to be resistant to the bacteriophage in the test tube. However, when grown on agar plates the strain revealed plaque formation, and by serial filtration of broth subcultures a bacteriophage highly potent against stock laboratory cultures was again recovered. On March 31, at 3:30 p. m., a catheterized specimen of urine was taken. Cultures of this yielded 70,000 colonies per cubic centimeter of urine. The organism was found to be resistant to the bacteriophage in the test tube.

Immediately after the collection of the last mentioned specimen the bladder was irrigated with boric acid solution. On April 1 at 9 a. m. a solution of acriflavine base was left in the bladder, and on April 2 another irrigation with boric acid was given at noon. The administration of potassium citrate, which had been interrupted on March 27, possibly because of some erroneous idea on the part of the physicians that the citrate might be incompatible with bacteriophage, was continued after March 30, and on April 1 it was supplemented with soda.

On April 5 at 8 a. m. the bladder was catheterized, and at 8:30 a. m. on the same day cystoscopy was done with the patient under nitrogen monoxide-oxygen anesthesia, another specimen of bladder urine being taken at this time. The cystoscopic examination gave essentially negative results. The first specimen of bladder urine (8 a. m.) contained many pus cells and moderately numerous bacilli in the sediment. Cultures yielded 1,500,000 colonies per cubic centimeter. These bacteria were found to be resistant to the special bacteriophage prepared for this patient and to twenty-one other races of colon bacteriophages in the laboratory collection. The second bladder specimen, taken at the time of cystoscopy (8:39 a. m.), was clear and contained no recognizable leukocytes. Only 4 bacilli were found in the microscopic smear of the sediment. Cultures yielded only 15,000 colonies per cubic centimeter.

The record of this patient illustrates a difficulty which may arise when a bacteriophage is used to treat urinary infection without adequate care in regulating the reaction of the urine. It is possible, however, for resistant variants to develop in the patient even when the reaction of the urine is intelligently controlled. This

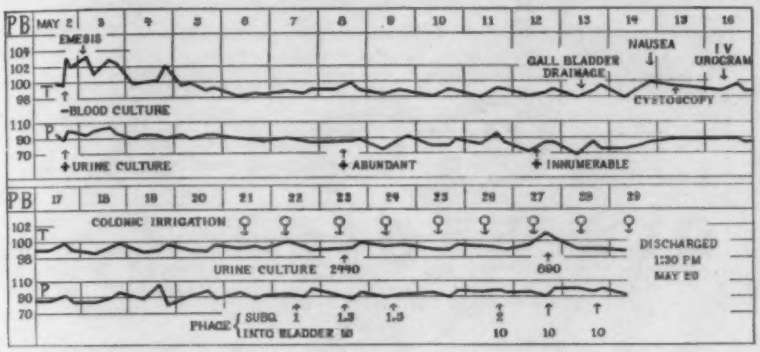

Chart 3.—Abridged clinical chart for P. B.

patient's condition was classified as postoperative cystitis with failure of bacteriophage therapy.

Case 3.—P. B., a white woman, aged 43, was admitted to the hospital on May 2, 1931, complaining of chills and fever lasting for about three days, associated with pain in the lower part of the abdomen and recurring at intervals of about three weeks during the last four months, sometimes associated with the menstrual period. A blood culture taken on May 2 was negative, but a culture of the urine yielded a growth of colon bacilli of the lactic acid variety, and there were moderately numerous leukocytes in the urine. The patient experienced what was apparently a typical attack of her disorder and improved by May 5. Numerous diagnostic procedures, including agglutination tests for tularemia, typhus and undulant fever, search for the organisms of malaria, basal metabolism tests and drainage of the gallbladder gave negative results. Roentgenograms of the kidneys, however, revealed a small, atrophic right kidney and a normal left kidney. Culture of the urine repeated on May 8 and again on May 12 gave abundant growth of colon bacilli. A series of colonic irrigations was begun on May 21, and potassium citrate, 15 grains (0.9 Gm.), was given on this day, preliminary to the use of bacteriophage which had been prepared. On May 22 three doses of potassium

citrate, total amount 60 grains (3.6 Gm.), were given, and the patient received a subcutaneous injection of 1 cc. of colon bacteriophage broth at noon. On the next day she was given a subcutaneous dose of 1.5 cc. and into the bladder 10 cc. of bacteriophage broth diluted with sterile saline solution. Bladder urine taken just preceding this instillation yielded 2,440 colonies of colon bacilli per cubic centimeter. The subcutaneous injection of bacteriophage was repeated on May 24 and on May 26, with instillation into the bladder on May 26, 27 and 28. Culture of the urine on May 27 yielded 890 colonies per cubic centimeter. The patient was discharged on May 29. She returned to the outpatient department and received intravesical instillations of bacteriophage on June 2, 4 and 16 and an intravesical instillation of 1:8,000 silver nitrate solution on June 23. From July 3 to 6 she was again in the hospital and, under nitrogen monoxide-oxygen anesthesia, received local injections of alcohol for relief of pruritus vulvae. Again in the outpatient department she received intravesical instillation of bacteriophage on July 14, 21 and 23. The specimen of bladder urine taken before treatment on May 27 yielded 890 bacterial colonies per cubic centimeter; that of June 2 yielded 3,780; that of June 4 yielded 620; that of June 15 yielded 7,270, and those of July 21 and July 23 gave no growth.

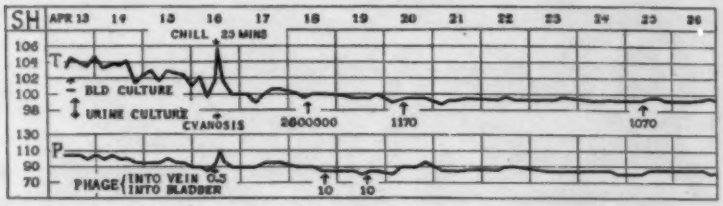

Chart 4.—Abridged clinical chart for S. H.

This patient's condition was classified as chronic recurrent pyelitis successfully treated with bacteriophage.

Case 4.—S. H., a graduate nurse, after exhausting service at private duty became ill on April 6, 1932, with painful and frequent micturition. On April 8 she had a severe chill and rise of temperature to 103 F. Constipation had been marked since March 30. She was admitted to the hospital on April 13. On this day a blood culture was found to be negative. Culture of the urine revealed innumerable colon bacilli of the lactic acid variety. Methenamine was given by mouth and also intravenously on April 13 and 14, after which it was discontinued. Potassium citrate was given, 40 grains (2.4 Gm.), on April 15, 20 grains (1.2 Gm.) on April 16, 40 grains (2.4 Gm.) on April 17, 35 grains (2.1 Gm.) on April 18, 60 grains (3.6 Gm.) on April 19 and 40 grains (2.4 Gm.) on April 20. The fluid intake was kept at a high level. Each specimen of urine was tested when fresh with blue and red litmus paper, and the morning and evening specimens were tested with phenol red and bromcresol purple with appropriate comparators to determine more precisely the hydrogen ion concentration. The dosage of the citrate was changed so as to keep the urine nearly neutral in reaction after April 15.

At 11:48 a. m. on April 16, an intravenous injection of 5 cc. of a 1:10 dilution of colon bacteriophage in asparagine was given intravenously in one hundred and thirty-five seconds. At 12:35 p. m., or forty-seven minutes after this injection

was started, the patient had a severe chill, complained of ringing in the ears and became very cyanotic. The rigor lasted for twenty-five minutes. At 1:30 p. m. the temperature was 105.8 F., the pulse rate, 110, and the respiratory rate, 20. At 2 p. m. there was profuse diaphoresis, and at 4 p. m. the temperature was 101.6 F. A catheterized specimen of urine obtained at 10 a. m. on April 18 was nearly neutral in reaction (p_H 6.9), and plate cultures showed 2,600,000 colonies of colon bacilli per cubic centimeter. Moderately numerous swollen bacteria were seen in the microscopic examination, but recovery of the bacteriophage from this urine by serial filtration of broth cultures was not attempted. At 6 p. m. on this day the bladder was irrigated with 1 liter of boric acid solution, and then 10 cc. of bacteriophage broth diluted with saline solution was introduced into the bladder and retained until 9 p. m. The urine voided at 9 p. m. was clear. On April 19 at 3 p. m. the bladder was again irrigated with a liter of boric acid solution, and bacteriophage broth was left in the bladder as before. On April 20 at 9:30 a .m. a catheterized specimen of urine was obtained and examined. The cultures brought to development 1,170 colonies per cubic centimeter of urine. After the taking of the specimen, the bladder was irrigated with a liter of boric acid solution which returned clear. The patient was comfortable and was up in a chair for a short time on this day. The bladder was irrigated with a liter of saline solution on April 21 and with a similar quantity of boric acid solution daily from April 22 to 28, inclusive. Preceding the irrigation on April 25, a urine specimen was taken for culture, and it yielded 1,070 colonies per cubic centimeter. Some of these colonies presented marginal defects, indicating the presence of active bacteriophage. Shortly after her discharge from the hospital on April 28, the patient returned to duty as a nurse.

On May 16 and again on December 5 bacteriologic examination of her bladder urine showed it to be free from bacteria. This patient's condition was classified as acute pyelitis with successful outcome of treatment confirmed by bacteriologic examination.

COMMENT

From the numerous cases of urinary infection we have selected these 4 as examples of success and of failure in acute and in chronic forms of this disorder. Pyelitis does not ordinarily present a serious threat to the life of the patient, and frequently it may permit a moderate amount of efficient activity. On this account, the patient and perhaps also his physician may not care to make too great a sacrifice in order to eradicate the infection. It is also evident that some urinary infections with colon bacilli are due to strains for which active bacteriophages are not now available. Furthermore, it sometimes happens that the infecting bacterial strain, at first susceptible to lysis by bacteriophage, later acquires a resistance to this agent. We do not, therefore, regard bacteriophages as panaceas for urinary infections with the colon bacillus. The hasty application of these agents without consideration of their limitations may be expected to lead to frequent disappointment. Particularly will this be the case when they are applied without adequate fluid intake and without attention to the chemical reaction of the urine, with simultaneous use of internal urinary antiseptics such as methenamine or in combination with repeated superfluous cystoscopic and ure-

teral instrumentation. On the other hand, when employed with intelligence and care and adequately controlled by continued laboratory studies throughout the course of treatment, the bacteriophages may often be of help and occasionally appear to bring about a dramatic favorable result.

SUMMARY

1. The results of bacteriophage treatment of urinary infections with colon bacilli have been highly irregular.

2. Some failures appear to be explained by the presence of resistant bacterial strains or bacterial strains which acquire resistance during the course of treatment.

3. Many failures in our series have obviously been due to a lack of sustained interest and of adequate sympathetic cooperation on the part of the patient, the clinician and the bacteriologist.

4. The technic of administration of bacteriophage and the adequate control of accessory therapeutic measures play a large part in determining success or failure.

5. Properly applied in properly selected cases of urinary infection, the bacteriophages add something of real value to the therapeutic armament in the urologic field.

ABSORPTION OF DEXTROSE AND WATER BY THE SMALL INTESTINE AND THE COLON

AN EXPERIMENTAL STUDY

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NEW ORLEANS

In view of the great importance in the practice of medicine of an adequate understanding of the normal processes of absorption from the gastro-intestinal tract, one is rather surprised to find that many hiatuses exist in the knowledge of this function—hiatuses that involve rather basic considerations. This is particularly true with reference to the absorptive activities of the large bowel, concerning which comparatively few facts are known for certain and much of the experimental investigation of which is inconclusive.

No one can question the ability of the large bowel to absorb certain substances, e. g., certain anesthetic substances, because of the characteristic train of symptoms which follow their administration and which could occur in no way other than as a result of absorption. Thus, one who has even once seen rectal anesthesia from ether or avertin has seen spectacular and incontrovertible evidence of specific colonic absorption.

Unfortunately, however, from the point of view of a knowledge of the colonic absorptive function, many of the other substances which the physician would like on occasion to introduce into the rectum for absorption produce no such spectacular or specific effects as are produced by drugs of the anesthetic type, and in dealing with the possibility, likelihood or extent of absorption of such substances resort must be taken to indirect methods, precise scientific calculations and an ample series of control observations.

That the rectum and colon are capable of absorbing significant quantities of water and certain simple salts, such as sodium chloride, sodium bromide, ammonium chloride and sodium iodide, seems to be generally, though not universally, admitted.

The ability of the rectum and colon to absorb the common, simple sugar, dextrose, however, is much doubted by many investigators, despite numerous excellent experimental efforts to settle the matter and a universal agreement that occasionally rectal administration of dextrose would be highly desirable clinically if it could be shown to be feasible.

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CRITICAL REVIEW OF PREVIOUS FINDINGS AND METHODS OF INVESTIGATION AS RECORDED IN THE LITERATURE

Exhaustive reviews of the literature on this subject have appeared in print, notably the recent excellent one of Ebeling,[1] and no good purpose would therefore seem to be served by a mere repetition of previous experimental findings according to author and year of publication. Inasmuch, however, as the experimental findings have been by no means conclusive, first, because the actual results obtained by similar methods of study but by different investigators have yielded almost diametrically opposite conclusions and, second, because in many instances the methods of experimentation have been open to more or less obvious and serious fundamental criticism, it seems desirable, even at the risk of repetition, to marshal again the results of previous investigators, but arranged in such a manner as to expose possible sources of error, and arrive, if possible, at a tentative conclusion which will, so far as possible, reconcile apparent discrepancies.

In general, two methods of attack have been used in investigating the problem: (*a*) the indirect and (*b*) the direct.

In the indirect attack, dextrose solutions of known concentration have been introduced into the large bowel by way of the anus in human beings and experimental animals, and the absorption of the dextrose has been measured by repeated estimations of the blood sugar or by repeated measurements of the respiratory quotient.

In the direct attack, solutions of dextrose of known concentration have been introduced into the rectum in human beings or into segments of intestine isolated at laparotomy under general anesthesia in animals, and later have been recovered and analyzed, the difference in amount between the injected and the recovered dextrose being taken as the measure of the absorption—the "wash-out method."

Results Obtained by Indirect Methods.—Method Based on Estimations of Blood Sugar: The greatest volume of experimental evidence has been collected on two assumptions: (1) that the blood sugar content necessarily increases whenever absorption of dextrose occurs from any part of the gastro-intestinal tract, and (2) that the blood sugar value is a function of dextrose absorption—that when absorption of dextrose occurs at a given rate the blood sugar value shows a definitely corresponding increase.

1. Some investigators have drawn conclusions from estimations of the peripheral venous blood sugar.

1. Ebeling, W. W.: Absorption of Dextrose from the Colon, Arch. Surg. **26**:134 (Jan.) 1933.

Using human subjects, Tallermann [2] injected 180 cc. of 33 per cent dextrose solution slowly into the rectum, and found that slight slow increases in the peripheral blood sugar occurred.

Varela and Rubino [3] gave retention enemas of 40 per cent dextrose solution to human beings, and concluded from peripheral blood sugar determinations and from urinalyses that minute amounts of dextrose were soon absorbed, but that the solution was not tolerated long and was soon expelled.

Franke and Wagner [4] introduced 25 Gm. of dextrose in the form of 50 per cent solutions into the rectum in dogs and determined the peripheral blood sugar level at the end of fifteen, thirty, forty-five and sixty minute intervals. These authors found little, if any, effect on the blood sugar level.

Levi [5] injected 500 cc. of solutions of dextrose varying in strength from 10 to 16 per cent into the colons of (1) normal men during fasting, (2) diabetic patients and (3) patients recently subjected to major surgical operations, and found that peripheral blood sugar estimations indicated individual differences in absorptive power, but that in general only small quantities of dextrose seemed to be absorbed.

Pressman [6] introduced 33 per cent solution of dextrose into the rectum in human beings, and found that this caused a decrease in the peripheral blood sugar.

De Takáts [7] found that the introduction of large quantities of 5 per cent solution of dextrose under the skin or into the mouth caused increases in the peripheral blood sugar, whereas the introduction of such a solution directly into the blood stream caused a decrease in the peripheral blood sugar during a period of two hours.

Scott and Zweighaft [8] examined the peripheral blood sugar level in medical students following rectal administration of hypertonic solutions of dextrose. They found no increase in the blood sugar after the

2. Tallermann, K. H.: On the Rectal Absorption of Glucose, Quart. J. Med. **13**:356 (July) 1920.

3. Varela and Rubino: Rektale Dextrose Zufuhr und Blutzucker, Med. Klin. **18**:831, 1922.

4. Franke, W., and Wagner, R. J.: Studies on the Fermentable Blood Sugar After Parenteral and Rectal Administration of Glucose, J. Metab. Research **6**:375, 1924.

5. Levi, D.: A Note on the Glucose Enema and Its Value in Postoperative Treatment, Brit. J. Surg. **15**:282, 1927.

6. Pressman, J. J.: Absorption of Glucose per Rectum, Am. J. M. Sc. **179**: 520, 1930.

7. de Takáts, G.: Push Fluids; Surgeon's Postoperative Order, Am. J. Surg. **11**:39, 1931.

8. Scott, E. L., and Zweighaft, J. F. B.: Blood Sugar in Man Following the Rectal Administrations of Dextrose, Arch. Int. Med. **49**:221 (Feb.) 1932.

administration of 180 cc. of a 15 per cent or a 30 per cent solution, a decrease of about 10 mg. per hundred cubic centimeters of blood after the administration of 200 cc. of a 10 per cent solution and a decrease of 7.5 mg. per hundred cubic centimeters of blood after the administration of 400 cc. of a 10 per cent solution.

Such experimental results are inconclusive for at least three reasons:

(*a*) Authorities are not agreed that the peripheral blood sugar varies in parallelism with the intestinal absorption of dextrose.

Cori [9] concluded after investigating the alimentary absorption of dextrose that the peripheral blood sugar level cannot be used as a measure of intestinal absorption.

Ebeling [1] concluded that estimations of the blood sugar are not accurate criteria of the intestinal absorption of dextrose, at least when the rate of absorption is slow, i. e., that there is no correlation between the blood sugar level and the rapidity or the extent of absorption.

Magee and Reid [10] concluded, on the other hand, that the peripheral blood sugar level can be used as a measure of intestinal absorption. They found at a time when no intestinal absorption was occurring that the portal and systemic blood sugar values were practically identical, whereas within about three minutes after a solution of dextrose had been ingested the portal blood sugar showed an increase of approximately 20 mg. per hundred cubic centimeters, and that this general disproportion was maintained throughout the period of absorption; however, inasmuch as both levels rose, the systemic blood sugar level was as good an index of absorption as the portal level.

(*b*) Almost without exception, intensely hypertonic solutions have been used, and, reasoning from the established action of other hypertonic solutions in the intestinal tract, one would expect, at least as a primary action, abstraction of water from the intestinal capillaries or tissue spaces to occur rather than absorption of the solute. That this is exactly what does happen when hypertonic solutions are used is suggested by the accurate clinical observation that such solutions are irritating (i. e., their bulk soon becomes intolerable), and that they are expelled.

(*c*) Finally, judged purely on their own merits, the results are inconclusive inasmuch as some increase in peripheral blood sugar has been found by a number of investigators, no increase by others, and even a depression of the peripheral blood sugar by still others.

2. Recently several investigators, using experimental animals, have attempted to draw conclusions from estimations of the blood sugar in

9. Cori, C.: Mammalian Carbohydrate Metabolism, Physiol. Rev. **11**:143, 1931.

10. Magee, H. E., and Reid, E.: Absorption of Glucose from the Alimentary Canal, J. Physiol. **73**:163, 1931.

samples taken from the radicals of the portal system draining isolated loops of intestine in which solutions of dextrose had been placed.

Inasmuch as these experiments have been combined with observations by the "wash-out" or direct method, they can best be detailed under the heading of the latter a little later. These experiments have seemed to show that little if any absorption of dextrose occurs compared with that occurring in the ileum.

For the present it will suffice to mention some of the possible shortcomings of such a method:

(*a*) All such experiments involve anesthesia, laparotomy, trauma to the intestine and its blood vessels, some hemorrhage, and usually difficulty in obtaining adequate quantities of blood for proper analysis. Anesthesia and operative manipulations, at least, cause variations in the blood sugar level, as I shall demonstrate later by my own experiments.

(*b*) The experimental conditions involve the absorption of water and dextrose; since the dextrose is supplied in solution, obviously the absorption of a considerable amount of water vitiates quantitative estimation of the absorption of dextrose, for the concentration of dextrose which is taken as the measure of absorption is affected by the dilution, a simple fallacy but one which seems to have been completely overlooked.

(*c*) Such a method would fail entirely to show the absorption of dextrose if the absorption were sufficiently slow, for the experimental error in blood sugar analysis would mask it completely, and an amount of absorption which might be slight in an hour or two and after an extensive intra-abdominal operation might be considerable in a period of several hours, especially in a patient not subjected to laparotomy.

Method Based on Effects on the Respiratory Quotient: Other investigators have used the respiratory quotient to measure absorption.

Hari and Halasz [11] tied a ligature tightly about the ileocecal valve in dogs and after introducing solutions of dextrose through the rectum found only slight increase in the respiratory quotient.

In two experiments on human beings, Carpenter [12] administered retention enemas of 30 Gm. of dextrose in 500 cc. of physiologic solution of sodium chloride. Within two or three hours, the respiratory quotient changed from 0.02 to 0.05, and a considerable portion of the dextrose originally introduced could not be recovered by washing out the colon (17.5 Gm. in one case and 26.3 Gm. in the other).

That the respiratory quotient is a reliable measure of dextrose *utilization* is generally agreed, but that it is an utterly unreliable method

11. Hari, P., and Halasz, A. V.: Biochem. Ztschr. **88**:337, 1918.

12. Carpenter, T. M.: Human Metabolism with Enemata of Alcohol Dextrose, and Levulose, Washington, D. C., Carnegie Institution, publ. 369, 1925.

of determining the *absorption* of dextrose has been apparently well demonstrated. Furthermore, Brodie, Cullis and Halliburton [13] concluded from experiments in 1910 that increased consumption of oxygen might follow the introduction of ordinary distilled water into the bowel.

That the administration of dextrose to patients is not necessarily immediately followed by catabolism of this substance was shown by Koster and his associates.[14] They demonstrated that even when dextrose solutions were introduced directly into the blood stream the respiratory quotient was not altered if the injections were performed in the early days following an extensive surgical operation (the interpretation of this is that in such cases the injected dextrose is not rapidly and immediately catabolized).

Results Obtained by the Direct Method.—The direct or "wash-out" method would seem on first consideration to offer a rather easy solution to the problem.

1. Some of the early work in which this method of approach was used was done employing human beings and introducing the solution by anus.

Deucher [15] introduced 200 Gm. of dextrose into the rectum of a patient during a period of nineteen hours, after which he was able to recover only 46 Gm., or 23 per cent of the total amount.

Bingel [16] placed 35 Gm. of dextrose in the bowel of a series of diabetic patients and one hour later was able to recover 31 Gm. by washing out the colon.

Scott and Zweighaft [17] administered 10 to 30 per cent solutions of dextrose to medical students by rectum and recovered from 25 to 50 per cent.

The objections to these experimental observations are mainly three:

(*a*) Grossly hypertonic solutions were used, and hypertonicity probably hinders rather than facilitates absorption, as previously mentioned.

(*b*) Losses occurring as a result of unrecognized expulsion from the anus or regurgitation into the small intestine through the ileocecal valve would be falsely interpreted as due to colonic absorption.

(*c*) No allowance was made for the possible effect of dextrose-splitting bacteria or other dextrose-splitting agents in the bowel.

13. Brodie, T. G.; Cullis, W. C., and Halliburton, W. D.: J. Physiol. **40**:173, 1910.

14. Koster, H.; Collens, W. S., and Goldzieher, M. A.: Intravenous Injection of Glucose; Its Effect on Respiratory Quotient, Am. J. Surg. **8**:970, 1930.

15. Deucher, P.: Deutsches Arch. f. klin. Med. **58**:210, 1897.

16. Bingel, A.: Therap. d. Gegenw. **46**:436, 1905.

17. Scott, E. L., and Zweighaft, J. F. B.: Blood Sugar in Man Following the Rectal Administration of Dextrose, Arch. Int. Med. **49**:221 (Feb.) 1932.

2. By far the most impressive experimental work has been performed on animals under anesthesia and after laparotomy.

McNealy and Willems [18] reported absorption experiments in a series of fifteen dogs prepared as follows: (*a*) All food was withheld for from sixteen to eighteen hours; (*b*) anesthetization was produced with barbital and reenforced with a small amount of ether; (*c*) comparable loops of colon and ileum were isolated between ligatures, and glass cannulas were tied into the four ends of the isolated loops; (*d*) the isolated loops were thoroughly washed out with physiologic solution of sodium chloride, (*e*) from 50 to 75 cc. of 5 per cent dextrose solution was then introduced into each of the isolated loops; (*f*) the solutions were removed in toto by "washing-out" at the end of one-half hour; (*g*) similar amounts of 5 per cent dextrose solution were then introduced and washed out at the end of one hour, and (*h*) the solutions removed after one-half hour and one hour were then analyzed for sugar content. The venous blood draining from the loops was analyzed at the beginning and at the close of the observations.

The amount of dextrose lost from solutions introduced into the colon was small and within the limits of experimental error (from 3.4 per cent to 13 per cent); the amount of dextrose lost from the ileum was much greater (from 18 to 69 per cent). Analyses of the blood sugar level in the veins draining the isolated loops substantiated these conclusions, for in no case was there an appreciable increase of sugar in the blood draining from the colon, whereas in all cases there was a marked increase of sugar in the blood draining from the ileum.

Ebeling [1] used an experimental technic similar to that of McNealy and Willems. Dogs were used as experimental animals. Loops of intestine were isolated between ligatures at laparotomy under sodium amytal anesthesia, one loop consisting of the appendix and a segment of the adjacent ileum, and the other loop consisting of the colon and rectum. Glass cannulas were then tied into both ends of each loop. The intestinal segments were thoroughly flushed through and through with warm tap water. Measured amounts of warm 5 and 10 per cent solutions of pure bacto-dextrose were then introduced into the loops. Samples of blood were withdrawn from the femoral vein at intervals of one-half hour; samples of blood were taken from the ileal and colic veins before and after each period of observation. The sugar concentration was determined in every sample. At the end of each period of observation, the segments of intestine were thoroughly evacuated and flushed with 2,500 cc. of distilled water. The percentage recovery of dextrose was calculated after chemical analysis.

18. McNealy, R. W., and Willems, J. D.: Absorption of Glucose from Colon; Preliminary Study of Glucose Enema, Surg., Gynec. & Obst. **49**:794, 1929.

Ebeling concluded from his observations on twenty-four animals:

(*a*) Solutions of dextrose are absorbed only slowly and in small amounts from the entire colon of the dog, but much more rapidly and in larger amounts from the ileum.

(*b*) The absorption of dextrose from a 10 per cent solution is slightly more rapid than that from a 5 per cent solution, but the difference in degree of absorption is not great.

(*c*) The rate and the amount of absorption of dextrose from the colon is much greater in hypoglycemic than in normal animals and in the former may approach the normal rate of absorption from the ileum.

(*d*) The blood sugar values show no direct correlation with the rate and the amount of intestinal absorption, especially when the latter is small.

(*e*) The water in a solution of dextrose is absorbed less rapidly by the colon than is tap water to which no dextrose has been added, i. e., the presence of dextrose hinders the absorption of water.

It seems on first consideration that the experiments of McNealy and Willems and Ebeling should definitely settle the question of colonic absorption. They found little absorption from the colon in a reasonably large and most carefully manipulated series of animals in which details of technic were carefully observed.

The only objections to complete acceptance of the findings are:

(*a*) What is found in a dog may not find direct application in man. This is an objection common to many experimental studies, and in this instance should probably carry little weight.

(*b*) The observations were made under anesthesia and after extensive intra-abdominal surgical manipulations. However, it should be remembered that these factors largely cancel out when absorption from the colon is compared with that from the ileum in the same animal at the same time.

(*c*) Absorption rates were compared based on segments of intestine which were apparently not measured with accuracy and which consequently may not have presented comparable surface areas. Obviously the unit of measurement which should be used as an index of absorption involves surface area and time; viz., a given portion of the intestinal mucosa absorbs at the rate of a certain number of cubic centimeters or grams of a given substance per unit area per unit of time. Any experiment which compares unknown surface areas yields results which may tell the truth or the direct opposite or any intermediate degree of truth or falsehood, depending on circumstances.

(*d*) The trauma to the intestine was maximal. Not only were loops of intestine brought out of the abdomen, isolated and ligated and

cannulas inserted, but they were then subjected to a thorough washing; therefore not only the outside or peritoneal coat was subjected to direct trauma but the mucosal surface as well. The effect of even slight trauma on the motility of the intestine is well known to all abdominal surgeons; mere opening of the abdomen causes cessation of practically all peristalsis, and the normal motility does not return for many hours after the abdomen has been carefully closed again. It seems reasonable to suppose that the absorptive function may suffer as great or even greater disturbance. If so, it would not seem mere wild conjecture to assume that different parts of the intestinal tract may show differential susceptibility. As a result of continued washing, the colon and rectum, which normally contain solid or semisolid material, may well undergo greater disturbance of absorptive function than the ileum, the contents of which are normally liquid. In this connection it should also be remembered that technically manipulation of the colon is more difficult and therefore more likely to be productive of trauma than is manipulation of the ileum, owing to the nature of its position and its attachments.

(*e*) The fact that under conditions of continued hypoglycemia Ebeling found the colon able to absorb dextrose nearly as well as the normal ileum certainly suggests that the colon is not lacking in ability to absorb.

EXPERIMENTS

The experiments about to be described were undertaken under the stimulation of the work of McNealy and Willems previously reviewed. They had already been completed before the appearance of Ebeling's excellent article. Had the results of these experiments agreed with those reported by McNealy and Willems and Ebeling, I should perhaps never have attempted to place them on record.

My work was undertaken, as already suggested, because of a conviction that all previous work not based on actual analysis of injected and recovered dextrose (the direct or "wash-out" method in experimental animals, in which all factors could be carefully controlled) was subject to so many discrepancies as well as differences of interpretation as to leave the question of colonic absorption practically unanswered. Furthermore, I felt that the work of McNealy and Willems, though highly suggestive of an answer, was not quite convincing, mainly because they allowed only a relatively short period of absorption after a period of intense trauma and then failed entirely to make their comparisons in terms of the amount of absorption per unit of surface area per unit of time.

Furthermore, inasmuch as these authors had used a barbituric acid derivative as an anesthetic agent and had then used blood sugar estimations as an essential part of their experimental observations without

investigating the effect of the drug itself on the blood sugar, it was felt that this matter should be subjected to observation.

Still further, in order to obviate, so far as possible, the factor of mucosal trauma due to repeated washings, I planned to allow absorption to occur in the presence of the normal intestinal contents; thus it became essential to determine the error introduced by the dextrolytic action of the normal contents.

Especially, I planned to allow a longer period of absorption—four hours instead of the one-half hour and one hour allowed by McNealy and Willems in order to reduce experimental error to a minimum.

The following technic was the common denominator of all of the experiments:

Presumably normal, full-grown mongrel dogs of various sizes were used as experimental material. Previous to the time of experimentation, the animals had been fed ordinary kennel rations. They underwent no period of preliminary fasting or other preliminary preparation of the intestinal tract. They were anesthetized by injecting into the external jugular vein a dose of sodium barbital computed on the basis of 0.3 Gm. of the drug per kilogram of body weight. Surgical anesthesia was induced by this dosage in most cases within from five to eight minutes. If at the end of ten minutes the animal was not entirely anesthetic, a small amount of ether was administered by inhalation to the point of anesthesia. The animal's abdomen was then opened by means of a 2 or 3 inch (about 5 or 7 cm.) low paramedian incision.

Specifically, the experiments were divided into four series, which were planned to answer the following questions:

1. To what extent are the normal contents of the ileum and colon capable of splitting artificially prepared dextrose solutions when acting at body temperature for a given interval of time?

2. Does sodium barbital in anesthetic doses itself have an effect on the blood sugar?

3. Do laparotomy and extensive intra-abdominal manipulation have an effect on the blood sugar?

4. To what extent do the various parts of the intestine absorb dextrose and water from isotonic and hypertonic dextrose solutions?

Lysis of Artificially Prepared Dextrose Solutions by Intestinal Contents.—Five dogs were used. The entire colon and rectum were isolated between ligatures after the mesenteric blood supply was controlled. A corresponding segment of the terminal portion (about 40 cm.) of the ileum was isolated between ligatures and removed in the same manner. The content of each of these segments was then expressed into a separate beaker. Exactly 150 cc. of an accurately prepared 5 per cent solution of bacto-dextrose solution was then added to each of the two solutions. The beakers were placed in the incubator at 37.5 C. for four hours. The solutions were then carefully filtered, measured and

analyzed by Benedict's quantitative urinary sugar method for dextrose content. The loss of dextrose was calculated.

Results: Both colonic and ileal contents showed dextrolytic properties, but the colonic contents showed more active lytic properties than the ileal contents. The average recoveries were as follows: for the colon, recovery of 87 per cent of the added dextrose; for the ileum, recovery of 96.6 per cent of the added dextrose.

There is little opportunity for direct comparison between these results and the results obtained by previous investigators, for the experimental conditions have not been comparable.

Bingel[19] found that when dextrose was added to fecal material and incubated the loss was almost as great as that which occurred when dextrose was placed in the bowel of a living diabetic patient.

Boyd and Robertson[20] incubated dextrose solutions with colon bacilli and concluded that the amount of dextrose disappearing as a result of bacterial action was insignificant.

In 1925, Cori[21] incubated measured quantities of dextrose in segments of the small intestine at 37 C. for periods of from three to five hours, and concluded that the loss of dextrose due to bacterial action was so small as to be negligible.

Pressman[6] found that nearly 90 per cent of the dextrose in a given solution was destroyed by incubation with feces for seven hours.

Ebeling[1] incubated 75 cc. of a 4.7 per cent solution of dextrose in an excised and washed segment of the colon at 37.5 C. for two hours and estimated the loss of dextrose as a result of the incubation at 2.6 per cent.

Effect of Anesthetic Doses of Sodium Barbital on Blood Sugar.—In a series of twenty dogs Folin and Wu blood sugar analyses were performed: (1) just before the administration of anesthetic doses of sodium barbital and (2) again about five minutes after surgical anesthesia had been induced by this drug.

Results: Fifteen of the twenty dogs, or 75 per cent, reacted with a relative hyperglycemia. The increase varied between 2.5 mg. and 50.1 mg. per hundred cubic centimeters, with an average of 15.46 mg.

The remaining five animals reacted with a relative hypoglycemia and showed decrements ranging between 1.1 mg. and 9.5 mg. per hundred cubic centimeters, with an average of 6.24 mg.

From these findings it becomes evident that pharmacologically sodium barbital belongs to a group of drugs which in toxic doses characteristically produce hyperglycemia; included in this group are epinephrine,

19. Bingel, A.: Therap. d. Gegenw. **46**:436, 1905.

20. Boyd, F. D., and Robertson, T.: Scottish M. & S. J. **18**:193, 1906.

21. Cori, C. F.: Fate of Sugar in Animal Body; Rate of Absorption of Hexoses and Pentoses from Intestinal Tract, J. Biol. Chem. **66**:691, 1925.

picrotoxin, quinine and probably many others. The exact mechanism by which this particular drug produces its hyperglycemic effect can be determined only by further experimentation, as the hyperglycemic mechanism does not seem to be the same for all drugs.

This interesting pharmacologic observation is not recorded with the purpose of suggesting that false conclusions have necessarily been drawn when experimental work has been performed under the anesthetic action of the barbiturates; not only may other barbiturates, like amytal, fail to show this action, but presumably a normal blood sugar reading has been made after the administration of the drug. However, the possibility of serious error is suggested, and the phenomenon can at least be cited as evidence of the general instability of the blood sugar under experimental conditions.

Effect of Laparotomy and Intra-Abdominal Manipulation on the Blood Sugar.—In a series of seventeen dogs surgically anesthetized with sodium barbital the effect on the blood sugar of laparotomy and intra-abdominal manipulations was studied as follows:

Folin and Wu blood sugar determinations after anesthetization with sodium barbital were compared with a similar series of blood sugar determinations made after the abdomen had been opened and the colon and ileum had been ligated and cannulas tied in, as will be described in the discussion of the principal part of the experiment, which follows.

Results: All except two of the seventeen animals, i. e., 88 per cent, showed relative hyperglycemia as a result of the operative manipulations. The increases varied between 13.4 mg. and 92.7 mg. per hundred cubic centimeters, with an average of 39.36 mg.

The two animals excepted showed decrements of 12.9 mg. and 2.5 mg. per hundred cubic centimeters, respectively.

These results introduce the opportunity for rather interesting speculation as to the general value of blood sugar estimations as a measure of intestinal absorption under traumatic experimental conditions. If the peripheral blood sugar varies so greatly as a result of mechanical surgical manipulation alone, how can one hope to settle the question of intestinal absorption by a study at least of portal blood sugar values, since the mere obtaining of samples of blood for the determinations is inevitably associated with rather extensive handling of the intra-abdominal organs?

Differential Absorption of Dextrose and Water by the Colon, Ileum and Jejunum.—The "wash-out" method in combination with periodic examinations of the peripheral blood sugar was used in an attempt to determine the differential absorption of dextrose and water by the colon, ileum and jejunum.

A series of twenty dogs formed the basis for the conclusions; other animals were used but were not included in the final compilation of results because they did not yield a complete series of observations.

After the induction of anesthesia and the performance of laparotomy, as previously described, segments of intestine were isolated between tightly tied ligatures. Cannulas were inserted into these segments proximally only; the technic of inserting the cannulas consisted of (1) the introduction of a purse-string suture of linen just distal to the point of proximal ligation, (2) the introduction of a small glass cannula through the purse-string suture about the cannula (the purse-string suture was then tightly drawn) and (3) the introduction and tying of a second concentrically placed purse-string suture so as to preclude all possibility of leakage. The cannula was then connected by a short piece of rubber tubing to a short buret of large bore (50 cc. syringe barrel). The buret was held in a vertical position just above the animal's abdomen by means of a buret clamp. All of the manipulations were performed as rapidly and with as little trauma as possible; laparotomy pads wet with warm saline solution were freely used, and the greatest care was taken to prevent chilling of the abdominal contents and undue exposure to the air. As soon as these relatively simple manipulations had been made, the abdominal incisions were closed by means of several interrupted "through and through" sutures, and the animals were not disturbed thereafter for the duration of the experiment except periodically to withdraw blood from the external jugular vein.

The animals were prepared in two series of ten animals each. In one series 10 per cent solutions of dextrose were used; in the other, 5 per cent solutions of dextrose were used. Bacto-dextrose was employed for the preparation of solutions throughout; the dextrose was accurately weighed on a good analytic balance, and the solutions were subsequently checked by titration.

In five animals in each series as much of the colon as could be isolated intra-abdominally was used for one loop, and a corresponding length of the lowest part of the ileum (about 40 cm.) was used for a second loop; the cecal appendage was not included in either loop. In the other five animals of each series a third loop consisting of a comparable portion of jejunum was also isolated. Thus, in five animals of each series two loops (colon and ileum) were used, and in the remaining five animals three loops (colon, ileum and jejunum) were used.

The experimental observations began as soon as the abdomen of each animal was closed and the burets attached. First a sample consisting of 5 cc. of blood was obtained from the external jugular vein. Then an accurately measured amount of dextrose solution was poured into each buret. At intervals of exactly one hour additional samples of blood were removed from the external jugular vein. The fluid level in the burets was maintained, as absorption occurred, by the addition of measured amounts of dextrose solution; thus variable but accurately measured amounts were introduced, depending on the capacity and absorptive reaction of the individual loop. At the end of four hours, the animals were killed, the abdomen was rapidly opened, the loops of intestine were cut away, the contents of the loops were carefully collected and measured, and the loops were carefully split longitudinally and their surface areas computed by mensuration.

All of the blood samples were immediately analyzed for sugar content by the method of Folin and Wu for blood sugar. All of the fluid collected from the intestinal loops was immediately measured, filtered through coarse filter paper and analyzed for sugar content by Benedict's method for urinary sugar.

Results: The amounts of water absorbed by the mucosa per hundred square centimeters of surface area per hour are revealed in table 1; each computation represents the average of ten observations for the colon and the ileum and five observations for the jejunum.

It is obvious that all portions of the intestinal tract (colon, ileum and jejunum) absorb water from both 5 per cent (isotonic) and 10 per cent (hypertonic) solutions of dextrose. From the 5 per cent or isotonic solution, however, relatively large quantities of water are absorbed, whereas from the 10 per cent or hypertonic solution much smaller quantities are withdrawn.

TABLE 1.—*Mucosal Absorption of Water from Aqueous Solutions of Dextrose*

Solution of Dextrose	Cubic Centimeters of Water Absorbed per Hour per Square Centimeter of Surface Area of Mucosa		
	Colon	Ileum	Jejunum
5%	11.46	6.18	26.36
10%	8.5	0.15	1.8

TABLE 2.—*Absorption of Dextrose*

Solution of Dextrose	Segment Absorbing	Grams of Dextrose Absorbed per Hour per Hundred Square Centimeters of Mucosal Surface Area		
		Colon	Ileum	Jejunum
5%	Colon and ileum	1.96	1.66	
	Colon, ileum and jejunum	1.36	0.55	150.0
10%	Colon and ileum	1.12	1.02	
	Colon, ileum and jejunum	0.98	0.78	165.0

Although the jejunum absorbs water freely and in large quantities from a 5 per cent solution, it takes relatively little from a 10 per cent solution. The ileum absorbs considerably less water than the colon from both 5 per cent and 10 per cent solutions of dextrose; from the 10 per cent solution the ileum absorbs water scarcely at all. The colon absorbs less than half as much water as the jejunum from a 5 per cent solution of dextrose but more than four times as much from a 10 per cent solution.

The quantities of dextrose absorbed by the mucosa per hour per hundred square centimeters of surface area are recorded in table 2. The figures are uncorrected for the dextrolytic action of the intestinal contents. If they are corrected according to the percentages obtained in the preceding preliminary experiments (incubation experiments), the results indicated in table 3 are obtained.

It is evident from these computations that the jejunum absorbs vastly more dextrose from 5 and 10 per cent solutions than does the colon

or the ileum; the jejunum, however, absorbs only insignificantly more dextrose from a 10 per cent solution than it does from a 5 per cent solution. The colon and ileum absorb dextrose from 5 and 10 per cent solutions, but they absorb less from a 10 per cent solution than from a 5 per cent solution. The absorptive powers of the colon and ileum for dextrose are practically equal, though the figures show that the colon absorbs somewhat more than the ileum; previous investigators had found that it absorbed less.

The peripheral blood sugar values are given in table 4. They tend to fluctuate as a function of the amount of intestinal absorption.

TABLE 3.—*Figures in Table 2 Corrected for the Dextrolytic Action of the Intestinal Contents*

Solution of Dextrose	Segment Absorbing	Colon	Ileum
5%	Colon and ileum	1.68	1.60
	Colon, ileum and jejunum	1.18	0.53
10%	Colon and ileum	0.98	0.98
	Colon, ileum and jejunum	0.85	0.75

TABLE 4.—*The Peripheral Blood Sugar Values During Active Absorption of Dextrose from Colon, Ileum and Jejunum*

		Milligrams of Sugar per Hundred Cubic Centimeters—An Average of 10 Observations			
Solution of Dextrose	Segment Absorbing	After 1st Hour	After 2d Hour	After 3d Hour	After 4th Hour
5%	Colon and ileum	143.0	151.7	143.3	121.2
	Colon, ileum and jejunum	168.0	188.7	190.3	181.8
10%	Colon and ileum	160.4	164.5	167.9	167.9
	Colon, ileum and jejunum	156.2	208.1	238.2	262.3

In all of the cases, at the end of one hour of intestinal absorption the peripheral blood sugar had increased significantly.

A consistently greater increase in peripheral blood sugar occurred when the colon, ileum and jejunum were absorbing than when only the colon and ileum were absorbing, as would be expected from the previously demonstrated relatively enormous absorptive power of the jejunum. This was true with respect to both 5 and 10 per cent solutions.

That the intestinal absorption of dextrose and the increase in the peripheral blood sugar do not vary in exact parallelism, however, is suggested by the fact that the blood sugar when computed for four hours does not show consistent increments from hour to hour, but rather shows fluctuations and at times even decreases. Conceivably in the cases in which decrements occur intestinal absorption may have been halted for some unknown reason, but it seems more reasonable to believe that

the variations represent the interplay of other factors which would vitiate the general parallelism between absorption and the increase in the peripheral blood sugar.

COMMENT

In view of the relative facility with which the colon absorbs water and, according to these experimental findings at least, dextrose as well, the prejudice which many surgeons have come to have against proctoclysis as a clinical method is not altogether easy to understand.

In the human adult the large intestine exclusive of the rectum and the anal canal is from 135 to 140 cm. in length and presents an average diameter of about 5 cm. or more; accordingly, a conservative estimate of its mucosal surface area on the basis of these figures is 2,110 square centimeters. Assuming that the human colon absorbs at the same rate as that of the dog, it is capable, according to the present experimental findings, of absorbing about 240 cc. of water and 30 Gm. of dextrose per hour from a proctoclysis of 5 per cent dextrose solution. These figures are conservative, and they do not include such absorption as might occur from the rectum.

Many persons, of course, are unsuccessful in the use of proctoclysis because in their adaptation of apparatus and solutions they disregard fundamental physiologic principles. If too large a retention enema is given it produces discomfort or actual pain and is likely to be expelled rather promptly. Similarly, when a "drip" proctoclysis is used if the receptacle used as a reservoir is placed more than about 18 inches (about 40 cm.) above the level of the anus and the solution is allowed to flow into the bowel more rapidly than it can be absorbed, an incompatible amount of pressure is likely to develop within the colon, and the medical attendant is likely to find a leakage of solution about the rectal tube into the bed.

Probably the most fruitful source of difficulty, however, arises from the use of hypertonic solutions; as these experiments indicate, such solutions are inimical rather than conducive to absorption of water or dextrose. They undoubtedly tend by osmosis to withdraw fluid from the tissues; not only does this produce an effect diametrically opposite to the one desired, but the tissue fluid augments the bulk of the solution in the bowel, and the mere bulk is apt to stimulate expulsive efforts.

SUMMARY

1. The opinion that dextrose is absorbed only slightly, if at all, by the colon does not seem to be well supported by experimental evidence.

2. Much of the confusion in experimental results in the past has arisen from the fact that hypertonic solutions have been commonly used; the primary action of such solutions is probably an osmotic one according

to which water is withdrawn from the intestine and progressively dilutes the solution. From a practical point of view the outpouring of water is apt to increase the bulk of the solution to such an extent that the intestine is stimulated to expulsive movements. Such absorption of dextrose as does occur before isotonicity is established, i. e., from a hypertonic solution, must occur selectively and against osmosis.

3. Little dependence can be placed on experiments based on the assumption that the blood sugar level rises proportionately with the amount of intestinal absorption of dextrose. The parallelism may or may not exist, according to circumstances. The blood sugar level should be considered as a variable which is in a continuous state of flux and which is determined by the interplay of many different factors. Two factors previously ignored, which under experimental conditions, at least, may exert a profound hyperglycemic influence have been examined, and it has been found that:

(*a*) The general blood sugar level is elevated in more than three quarters of the cases by the administration of sodium barbital in doses sufficient to produce surgical anesthesia.

(*b*) Surgical manipulations also heighten the general blood sugar level in more than three quarters of the cases.

Variations of the local portal blood sugar, i. e., the blood sugar in the area draining loops of intestine which are actively absorbing dextrose solutions, are very likely of even less significance than the variations in the systemic blood sugar and this for a simple and obvious reason. Under the given conditions the coil of intestine absorbs dextrose and water, the dextrose being in solution in the water. If the local blood stream happens to absorb dextrose and water from the solution in a certain proportion each to each, i. e., in the proportion in which they exist in the blood at that point and if all other factors remain constant, it is obvious that no change occurs in the blood sugar concentration in spite of the absorption of the dextrose. On the other hand, at other differential absorption rates, the blood sugar might appear to decrease while actually increasing or might appear to increase while actually decreasing, depending entirely on whether the direction of the migration of the water is into or out of the intestine.

Accepting the apparently demonstrated fact that the colon absorbs water much more readily and rapidly than the ileum, the effect of this differential absorption would be to mask colonic absorption of dextrose and magnify the absorptive action of the ileum.

4. The respiratory quotient is an accepted measure of the utilization of dextrose, but no dependence can be placed on the respiratory quotient as a measure of intestinal absorption of dextrose. Consequently, con-

clusions based on variations of the respiratory quotient can be dismissed summarily as valueless.

5. Conclusions as to colonic absorption based on analyses of dextrose solutions first introduced into the intact intestinal canal through the rectum and then recovered by the same avenue are unreliable for two reasons: (*a*) It is probably impossible to control regurgitation of such solutions through the ileocecal valve and difficult absolutely to prevent regurgitation through the anus, thus preventing all loss not due to absorption, and (*b*) the factor of lysis by intestinal contents at body temperature is disregarded.

6. Although previous experiments using much the same technic as that used in the experiments herewith reported have seemed to show that the colon absorbs little dextrose in comparison with the ileum, I have been able to demonstrate, (*a*) by reducing trauma to an absolute minimum, (*b*) by using a relatively long period of observation and (*c*) most important of all, by comparing accurately measured equal areas of intestinal mucosa, that the colon absorbs dextrose as actively as the ileum and water in far larger amounts.

7. The present series of experiments indicates that the use by rectum of a hypertonic solution of dextrose is highly undesirable. From a 10 per cent solution, actually less dextrose is absorbed by the lower part of the intestinal tract than from a 5 per cent (practically isotonic) solution, and the hypertonic solution interferes markedly with the absorption of water as well.

8. Although, according to the present experiments, the lower portion of the intestinal tract under favorable conditions is capable of absorbing considerable quantities of dextrose and water, and although proctoclysis can therefore be regarded as of definite clinical value, the amount of absorption of dextrose which occurs low in the intestinal tract is only a fraction of that which occurs in the jejunum. Rectal administration of dextrose is therefore only a relatively inefficient substitute for oral administration and should be adopted only when, for one reason or another, oral administration is contraindicated.

THE VISCEROSPINAL SYNDROME: A CONFUSING FACTOR IN SURGICAL DIAGNOSIS

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In presenting this subject we realize that we are adding to the already voluminous writings on pseudopathology which have accumulated through the years, and we are fully aware of the futility of any presentation which is merely an addition to the store. However, if by the presentation of certain clinical observations we can stimulate discussion and further active investigation in a field which despite the literature is still somewhat uncharted, a definite contribution will have been made.

In the diagnosis of surgical conditions, acute or chronic, involving the viscera we are usually confronted with certain signs and symptoms which we consider characteristic. Pain, tenderness, nausea and vomiting, abdominal rigidity and distention comprise a chain which surgeons are prone to interpret as signifying pathologic involvement of the viscera. The fact that conditions remote from the apparent location of the disturbance—extravisceral conditions, let us say—may produce signs similar to those of pathologic involvement of the viscera is not always given due consideration.

Our attention was recently drawn to this subject by one of our associates, N. T. Ussher, who for a number of years has studied the relationship between certain chronic visceral disturbances and spinal curvatures. In a recent article Ussher,[1] following a careful search of the literature, made the interesting observation that the effect of certain skeletal abnormalities on the viscera is not generally recognized.

True, a number of writers, notably Dejerine,[2] Carnett,[3] Gunther and

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Read before the section on general surgery at the Sixty-Second Annual Session of the California Medical Association, Del Monte, Calif., April 24, 1933.

1. Ussher, N. T.: Spinal Curvatures—Visceral Disturbances in Relation Thereto, California & West. Med. **38**:423 (June) 1933.

2. Dejerine, J.: Semiologie des affections du système nerveux, Paris, Masson & Cie, 1914, p. 257.

3. Carnett, J. B.: The Simulation of Gall-Bladder Disease by Intercostal Neuralgia of the Abdominal Wall, Ann. Surg. **86**:747 (Nov.) 1927; Chronic Pseudoappendicitis Due to Intercostal Neuralgia, Am. J. M. Sc. **174**:579 (Nov.) 1927.

Kerr,[4] Nielsen[5] and others,[6] have repeatedly described syndromes due to pathologic changes in the nerve roots or trunks (at or near the spine), the chief symptoms of which have been pain and hyperesthesia of some area remote from the source. The cases reported have usually been classified as radiculitis, the radicular syndrome and intercostal neuralgia.

On careful study of about fifty cases which appeared to be caused by some derangement at or near the spine or involving the nerves of this region Ussher noted that the disturbances were not the simple peripheral nerve conditions which had been previously described but that they showed symptoms distinctly visceral as well. He has suggested the term "viscerospinal syndrome" as describing their origin and its bearing on their symptomatology.

In the past few years there have been considerable speculation and a large amount of investigative work on the relationship of the somatic to the visceral nervous system[7] from the standpoint of referred pain, tenderness and muscular rigidity, and several interesting theories have been propounded.

To go into all the details or to weigh the merits and demerits of the several theories at this time would avail us little since the various investigators[8] in no wise agree as to the mechanism involved. That there is a definite relationship between the viscera and the corresponding segmental distribution of nerves is held by Pottenger[9] who stated: "The segmental relationship which exists between an efferent visceral neuron and an afferent somatic neuron probably also exists between an afferent somatic and an efferent visceral neuron." He suggested that

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4. Gunther, Lewis, and Kerr, W. J.: The Radicular Syndrome in Hypertrophic Osteo-Arthritis of the Spine: An Analysis of Thirty Cases, Arch. Int. Med. **43**:212 (Feb.) 1929.

5. Nielsen, J. M.: The Radicular Syndrome, J. A. M. A. **88**:1623 (May 21) 1927.

6. Mayer, E. E.: Radiculitis: Its Diagnosis and Interpretation, J. A. M. A. **71**:353 (Aug. 3) 1918.

7. Morley, J.: Significance of Afferent Impulses from the Skin in the Mechanism of Abdominal Pain, Lancet **2**:1240 (Dec. 14) 1929. Robertson, George: Disturbed Reflexes; Their Significance in Acute Abdominal Disease, Surg., Gynec. & Obst. **43**:807 (Dec.) 1926.

8. Weiss, S., and Davis, D.: The Significance of Afferent Impulses from the Skin in the Mechanism of Visceral Pain, Am. J. M. Sc. **176**:517 (Oct.) 1928. Forbes, A.; Cannon, W. B.; O'Connor, J.; Hopkins, A. McH., and Miller, R. H.: Muscular Rigidity With and Without Sympathetic Innervation, Arch. Surg. **13**:303 (Sept.) 1926. Livingston, E. M.: The Skin Triangle of Appendicitis, Arch. Surg. **13**:631 (Nov.) 1926.

9. Pottenger, F. M.: Important Reflex Relationships Between the Lungs and Other Viscera, J. Thoracic Surg. **1**:75 (Oct.) 1931.

"there is a continuous flow of stimuli from the surface of the body inward to the viscera and from the viscera outward to the skeletal tissues."

Assuming for the moment that this relation exists, is it unreasonable to suggest that apparent visceral symptoms may have as their origin stimuli due to pathologic changes somewhere in the surface or skeletal structures? Is it unreasonable further to assume that, given a strong enough stimulus from some more remote region, actual disturbance in the visceral physiology could be brought about?

Let us consider for a moment an injury such as a strain of the muscles of the lumbar and dorsal region in which a few strands or fibers are torn. A traumatic myositis is set up with spasticity of the muscle. There may be little or no pain on ordinary movement, for, as Hoover [10] stated, unlike inflammation of other structures of the body, inflammation of a muscle is relatively painless on activation, providing the sheath or tendon is not involved.

This spasm sets up a reflex spasm in the abdominal musculature whether for the purpose of splinting the weakened back as suggested by some writers or for some other reason.

It is conceivable that irritation of the afferent neurons of this damaged muscle, depending on the location and extent of the damage, might be responsible for transmission of stimuli via one of the reflex pathways to the viscera, and that symptoms of nausea and vomiting, pain and distention might appear. The chain of symptoms thus produced might so exactly simulate those of actual visceral disease as to make the diagnosis of the true condition extremely difficult.

We are sure that the first reaction to such a glib statement of what is necessarily a complex mechanism will be to demand a proof of what is admittedly a rather amazing assumption.

Unfortunately, when dealing with a subject in which so little is known and so much is still speculation conclusive proof may be extremely difficult.

At the present time the experimental evidence concerning sympathetic and parasympathetic reflex mechanisms is somewhat confused, and we believe that in the light of present knowledge an adequate explanation of the phenomena which we have observed clinically cannot be reconciled with existing theories.

At the outset of this article we stated that we wished to present clinical data based on observation in the hope of stimulating further investigation. We shall present the histories of a few cases illustrating this syndrome.

10. Hoover, C. F.: Diseases of the Muscles, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Co., Inc., 1920, p. 527.

REPORT OF CASES

CASE 1.—A man, single, white, aged 39 years, was referred to our service with a tentative diagnosis of acute appendicitis. The patient stated that while pitching hay the day before the onset he felt a "catch" in his back which hurt him somewhat on lifting during the rest of the afternoon. The following morning at 5 a. m. he awoke with severe cramplike pain over the entire abdomen; the pain later localized in both lower quadrants. On admission the duration of this pain was ten hours.

Nausea and vomiting came on about one hour after the onset and persisted intermittently up to the time of admission. There was no bowel movement until late in the afternoon when a small amount was passed. The pain was increasingly severe on moving about.

Examination.—The examination revealed a well developed white man lying with knees drawn up, apparently in considerable pain. The head, neck and chest were normal. The temperature was 98 F., the pulse rate, 60; the respiratory rate, 20.

Abdomen: There was marked boardlike rigidity of the lower part of the abdomen. The right lower quadrant was tender on pressure. The kidneys were not palpable.

The lumbar and dorsal muscles were spastic and extremely tender on pressure.

Laboratory Examination.—The white cell count was 9,000 with 80 per cent polymorphonuclear leukocytes. The urine was normal; the Wassermann and Kahn reactions were negative.

Treatment.—Heat was applied to the dorsolumbar region and heavy strapping for support.

Progress.—The pain in the abdomen subsided rapidly; there was no further nausea or vomiting, and rigidity disappeared within twelve hours. The pain shifted to the thigh and down to the knees. The patient rapidly improved and left the hospital in a few days with no other complaint than that of slight tenderness in the back.

CASE 2.—W. C. F., a married man, aged 39, a plumber, had been perfectly well until the day before entrance when on lifting a heavy laundry tray he experienced a sharp pain in the lower part of the abdomen. The pain seemed to encircle the lower part of the abdomen and the back. Occasionally it was more severe in the right flank and radiated down the inner side of the right thigh. The pain in the lower part of the abdomen was continuous. He was seen in our office by the orthopedist who made a diagnosis of traumatic lumbar myositis. The patient received heat and massage to the dorsolumbar region. He stated that the muscles of his back were "tied in a knot." The pain became worse on walking home. During the day and night there were many attacks of colicky pain localized in the right flank, and that evening the patient was nauseated and vomited two or three times. These attacks were accompanied by writhing on the bed, profuse perspiration and almost uncontrollable pain. There was no urgency, frequency or other urinary symptoms.

Examination.—An examination made at 4 a. m. gave negative results except for the back and abdomen.

Back: The back presented bilateral muscular spasm, in which the lumbar muscles were extremely hard, tense, tender and painful.

Abdomen: The abdomen showed absolute boardlike rigidity, increased tenderness in the right flank, colicky spasms of pain localized on the right side in

both upper and lower quadrants and pain down the inner side of the right thigh. There were no palpable masses and no rebound tenderness; the abdomen was tympanitic throughout.

Laboratory Examination.—The urine was normal except for occasional red blood cells. A later specimen of urine showed a trace of sugar and a trace of albumin with no red blood cells. The white cell count was 10,800 with 88 per cent polymorphonuclears. A later count showed 10,900 white cells with 80 per cent polymorphonuclears.

The roentgenographic study revealed no shadow in the region of the kidneys or ureters. Careful straining of the urine disclosed no calculi.

Progress.—After a discussion of the probable diagnosis a seven strap support was applied to the dorsolumbar and lumbar regions, a small dose of morphine administered, and the patient put in a semi-Fowler position with the knees elevated to relax the lumbar muscles. When he awoke from the narcosis the colicky pain was entirely relieved, and the pain in the back was diminished. He was discharged from the hospital on the second day and after adequate physical therapy made a complete recovery. At the time of writing, one year after the attack, there had been no recurrence.

Case 3.—A white man, married, aged 48, was brought into the office complaining of severe cramplike pain in the lower part of the abdomen, nausea, vomiting and loss of appetite. He stated that the first attack came on two weeks previously and that he was awakened out of sleep. He had been moving some heavy farm machinery the day before and had strained his back. He stated that he vomited once on the day of the onset and that the abdominal pain was so severe that he was forced to remain in bed several days. Subsequently he improved somewhat and was able to be up and about, but on the day before admission while he was at work the pain and nausea returned. He had a poor appetite during the entire two weeks, and the bowels were sluggish.

Examination.—The examination revealed a small moderately well developed white man. The head, neck and chest were normal. The temperature was 98.6 F., the pulse rate, 70; the respiratory rate, 18. The abdomen was markedly rigid in both lower quadrants and moderately rigid in the upper part. There was tenderness in the right lower quadrant. Marked spasm and tenderness on pressure were noted over the right lumbar and right lower dorsal region. The patient could not stand up straight.

Laboratory Examination.—The white cell count was 6,000 with 65 per cent polymorphonuclears. The urine was normal, and the Wassermann and Kahn reactions were negative.

Treatment.—Application of heat to the dorsolumbar region and a tight back strapping were followed by relief from the abdominal pain in one hour. Further treatment with heat and massage was followed by complete recovery.

Case 4.—A white truck driver, married, aged 26, was referred to our service complaining of intermittent pain in the left flank radiating to the back and lower part of the abdomen. The patient stated that the pain was always worse after he walked or rode in a truck. Usually he felt well on rising, but after he got about the pain came on increasingly as the day wore on. Nausea occurred frequently during attacks of pain. He had lost 20 pounds (9.1 Kg.). The duration of the condition was two and one-half years in which he had made the rounds of physicians and cultists with no relief.

Examination.—The examination revealed tenderness high in the left lumbar region and in the lower left quadrant of the abdomen on deep pressure. The abdominal muscles were slightly rigid. The left kidney was not palpable. A cystoscopic examination showed that the mucosa of the bladder was normal. The left ureter was catheterized with difficulty using a number 4 (French) catheter. The urine gave negative results culturally. No evidence of tuberculosis was seen, and inoculation of guinea-pigs gave negative results. Pyelograms showed the kidney to be in normal position; no abnormality was seen. Filling of the renal pelvis reproduced the pain (voluntary statement) but more severe than ordinarily. A diagnosis of stricture of the ureter was made.

Treatment.—Dilation of the left ureter at first gave relief for a day or so; later these treatments were of no benefit even after dilation with a number 12 catheter. On recheck examination a number 5 catheter was passed and ascended with resistance. Attempts to withdraw it revealed that it was in the grip of a spastic ureter.

The patient was referred to the orthopedic department for a check up. Examination showed a spastic left dorsolumbar region with tenderness of the muscles on pressure and a short left leg. There was a moderate scoliosis. The heel was raised one-fourth inch (0.64 cm.), and muscle training was given. The pain left within a few hours, and within two weeks the patient could walk several miles without discomfort. The appetite returned and the patient regained 5 pounds (2.3 Kg.) in the first month. Two and one-half months later he was working and free from pain. The only recurrence he has had took place one day when he wore his old work shoes on which there was no heel correction.

Case 5.—A white man, aged 31, was seen at the office complaining of attacks of pain radiating along the third and fourth ribs on the right side, discomfort on motoring due to a tired back, vague abdominal distress, vomiting and gas in the intestines near the stomach. These attacks had occurred intermittently for ten years. Roentgenograms of the gastro-intestinal tract were negative. An appendectomy in which an essentially normal appendix was removed because of pain and hyperesthesia in the lower right quadrant gave no relief. Two years later symptoms of mild ureteral colic developed on the right side. These persisted from two to three weeks. A cystoscopic examination gave negative results except for a slight angulation of the right ureter slightly below the right kidney. The patient had come to Santa Barbara for his health three or four years before.

On examination by our orthopedist he was found to have a dorsal scoliosis and a short right leg. The right heel was raised one-fourth inch and muscle training was given, which relieved the abdominal symptoms in two weeks; all distress ceased in a month. One year later there was a mild recurrence, but the raising of the heel an additional one-fourth inch and more vigorous muscle training cleared up the symptoms satisfactorily. Recently when playing golf, wearing a new pair of shoes without the raised heel, the patient had a recurrence of the abdominal symptoms, which responded immediately to the correction.

COMMENT

The cases here presented are a few of the typical ones in the series studied; we believe that they illustrate definite visceral disturbances resulting from stimuli arising outside of the viscera themselves.

It is our belief that the mechanism of production of these symptoms is essentially the same whether they follow direct trauma due to sudden

straining of the back or result from the chronic strain due to scolioses or other spinal curvatures. Hoover, in his discussion of myositis, stated that ordinary stretching of a muscle is not necessarily productive of local pain but that continuation of the stretching produces an area painful and tender to pressure—a definite myositis. We stress the dorsal and lumbar myositis because this appears to be the common factor in our series, and while the fact may be merely coincidental, following therapy directed at correction of the myositis the symptoms in every case cleared up.

We believe that this group of cases does not fall into the group classified as intercostal neuralgias as they are at present understood, since according to Carnett and others who have written extensively on pseudo-appendicitis and pseudo-disease of the gallbladder intercostal neuralgias should be ruled out when rigidity of the abdomen and actual visceral disturbances are noted.

We believe that we have been able to rule out the psychalgias [11] in the cases studied. This seems particularly true in the last two cases reported.

We are not prepared at this time to say that these symptoms may be explained on the basis of a radiculitis. The early, at times almost spectacular, relief that follows physical therapeutic measures seems to speak against pathologic changes in the nerve roots as a causative factor. Further, if the myositis which was invariably present is a responsible factor, it directs attention toward the endings rather than toward the roots or trunks of the nerves.

We do not wish to have it understood that we regard conditions in the back as in any way productive of pathologic changes of the viscera, but basing our assumption on our observations we feel safe in concluding that there is most certainly a disturbance of the physiologic processes. Neither do we suggest that surgical intervention be always withheld in questionable cases pending orthopedic checking and physical therapy, as we all know that the delay may be disastrous when actual pathologic changes are present and present an atypical symptomatology. We are taught by various writers [12] on abdominal diagnosis that pain lasting over a period of six hours together with nausea and vomiting and a rigid tender abdomen usually denotes pathologic changes in the viscera. It is not the purpose of this article to deny the truth of that

11. Pratt, J. H.; Golden, L. A., and Rosenthal, J.: The Psychalgias, J. A. M. A. **98**:441 (Feb. 6) 1932.

12. Cope, Zachary: The Early Diagnosis of the Acute Abdomen, New York, Oxford University Press, 1928. MacKenzie, J.: Symptoms and Their Interpretations, ed. 4, London, Shaw & Sons, Ltd., 1920.

dictum but rather to correct a more or less rule of thumb that "usually" means "always."

Finally to those who, like ourselves, after carefully evaluating a chain of symptoms, have opened an abdomen and removed an unoffending appendix, performed a fixation on an innocent if malposed kidney, repeatedly dilated an apparently strictured ureter or explored and found a normal gallbladder we wish to offer what appears to us a plausible reason for the symptoms in a few of these cases.

Santa Barbara Clinic.

OBSTRUCTION OF THE SUPERIOR VENA CAVA

AN EXPERIMENTAL STUDY

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ST. LOUIS

The clinical features of obstruction of the superior vena cava have been discussed by Ehrlich, Ballon and Graham.[1] As a review of the literature revealed no references to experimental studies of this condition in laboratory animals, a series of experiments were undertaken in which the superior vena cava was obstructed above, below or including the azygos vein. The object of the experiments was, primarily, to determine the tolerance of animals to occlusion of the superior vena cava, to measure the effects on venous pressures and to trace the paths of collateral circulation. Additional observations were made to determine the immediate effects of obstruction of the superior vena cava on the arterial blood pressure.

EXPERIMENTAL METHOD

Dogs were anesthetized with ether, positive pressure with the intratracheal technic being employed. An intercostal incision was made aseptically on the right side of the chest, usually through the fourth intercostal space. The superior vena cava (the azygos vein in some instances) was approached transpleurally and exposed by blunt dissection. When the vessel had been cleansed for a distance of about 2 cm., it was doubly ligated at two points and divided between ligatures. The wound was closed by encircling interrupted heavy silk sutures about the two ribs adjacent to the wound. The lungs were inflated as these sutures were tied. The overlying muscles and the skin were then closed in layers.

Obstruction Above the Junction with the Azygos Vein.—This was accomplished in the manner just described in seven dogs.

Obstruction Below the Junction with the Azygos Vein.—In two dogs an attempt was made to occlude the superior vena cava below the point of junction with the azygos vein. As both of these dogs died within a few minutes, no further attempts were made to produce obstructions at this point.

Obstruction Including the Azygos Vein.—A two stage obstruction of the superior vena cava and the azygos vein was successfully accomplished in two of three experiments. In the first of these the azygos vein was obstructed in a preliminary operation. Seven weeks later a second stage operation was performed, at which time the superior vena cava itself was obstructed. This dog died within one hour. In the two dogs surviving the immediate effects of total obstruction of the superior vena cava produced in two stages, the superior vena cava was first

From the Medical and Surgical Chest Service of Barnes Hospital and the Department of Surgery of Washington University School of Medicine.

1. Ehrlich, William; Ballon, H. C., and Graham, E. A.: Superior Vena Caval Obstruction, with Consideration of Possible Relief of Symptoms by Mediastinal Decompression, J. Thoracic Surg. **3**:352 (April) 1934.

obstructed above the level of the azygos vein. The second stage procedure, consisting of the obstruction of the azygos vein, was performed twenty-three weeks later in one dog and twenty-eight weeks later in the other.

EXPERIMENTAL RESULTS

General Observations.—Immediately after the superior vena cava was obstructed above the azygos vein, the dogs showed marked cyanosis of the tongue and the oral mucosa and injection of the conjunctivae. They recovered from the anesthetic slowly, and some of them were stuporous for many hours. The respirations were slow and deep.

Six of seven dogs with occlusion above the junction of the azygos vein recovered from the immediate effects rather rapidly, so that within twenty-four hours the cyanosis had practically disappeared. They continued to appear listless for several days, refusing food and losing weight. Dilated veins appeared over the thorax and the upper part of the abdomen, and hematomas usually formed in the thoracic wounds. Within a week or ten days the dogs' appetites improved, and eventually three of the seven became active, well nourished, normal appearing dogs.

Two of the dogs died of empyema (within thirteen or fourteen days), and one of a wound infection and extensive thrombophlebitis (on the twelfth day). The only dog that failed to survive the immediate effects of the obstruction lived only two days, and there were no postmortem observations to explain its death.

Of the three dogs that regained their health, one was killed for further study after thirty days, and the other two were subsequently subjected to obstruction of the azygos vein.

In the two dogs in which obstruction below the point of junction of the azygos vein had been performed, a slow, deep respiration, followed by gasping breathing, developed. The upper part of the body was deeply cyanotic. Death was apparently due to respiratory failure.

The dog that had been subjected to obstruction of the superior vena cava after a preliminary obstruction of the azygos vein also died with deep cyanosis and failure of respiration. Cyanosis did not develop following obstruction of the azygos vein, even in the animals previously subjected to occlusion of the superior vena cava.

A serosanguineous pleural effusion developed in the first dog which survived the immediate effects of a total occlusion produced in two stages. The fluid was aspirated on three occasions, from 190 to 500 cc. being removed. The dog eventually died of bilateral empyema twenty-one days after the second stage procedure. The second dog, in which total obstruction was eventually performed, became well and active. He was finally killed for study at the end of thirty-six days.

Development of Pleural Effusions.—Except in two dogs that died of empyema, pleural effusions did not develop in the dogs in which

obstruction above the azygos vein had been carried out. In the only dog that was subjected to preliminary obstruction of the azygos vein a sanguineous effusion developed, from which he recovered within two weeks. At the time of the second operation for obstruction of the superior vena cava itself (seven weeks after the obstruction of the azygos vein) the fluid had been completely absorbed.

Bilateral pleural effusions developed in the two dogs with obstruction of the azygos vein and of the superior vena cava. In the case of the first dog the effusion became infected, and the dog died of bilateral empyema. The second dog regained good health, but when he was killed at the end of thirty-six days, postmortem examination revealed the presence of 200 cc. of clear brownish fluid in the right pleural cavity and 100 cc. in the left. The pleural fluid cannot be said to be due entirely to the venous obstruction, because the trauma incident to the opening of the pleura and the formation of a raw surface at the site of the ligation of the vein undoubtedly contributed. However, it is clear that pleural fluid is not absorbed as readily when both the superior vena cava and azygos vein are obstructed as when the azygos vein alone is obstructed or when the site of the occlusion of the superior vena cava is above the level of the azygos vein.

Effect on Venous Pressures.—Venous pressure readings were obtained by inserting a needle into the external jugular vein and measuring the height of the column of blood in an attached vertical 4 mm. glass tube. The vein was first exposed by cutaneous incision and blunt dissection. The pressure before operation varied between 4 and 13 cm. of blood. The high pressures sometimes noted were probably caused by the struggling of the animals, although they were under ether anesthesia when the pressure readings were taken. Venous pressure readings taken on four dogs immediately after obstruction of the superior vena cava (above the azygos vein) were found to average 100 per cent higher than the preoperative readings. Three readings taken during the first nine days were found to be 65 per cent higher than the original readings, but three readings taken from fourteen to twenty-nine days after the operation showed no significant average increase above the preoperative venous pressures.

The venous pressure after obstruction of the superior vena cava and the azygos vein was obtained for two dogs. The original reading in the first animal was 6 cm. The pressure immediately after the first stage procedure was 18 cm.; fifteen days later, 11 cm., and seven days after the second stage procedure, 16 cm. (an increase of 167 per cent). No preliminary reading was taken on the second dog. However, thirty-six days after the second stage operation (obstruction of the azygos vein) the pressure in the femoral vein (5 cm.) was compared with that in the

jugular vein (10 cm.). The pressure in the obstructed venous circulation was therefore 100 per cent higher than that in the nonobstructed vein, but even this pressure was within the limits of normal observed in some of the other animals.

The findings suggest that in obstruction above the azygos vein the venous pressure is definitely increased, but that as a result of collateral circulation it may eventually become normal. In the case of total obstruction the venous blood pressure was definitely elevated for at least thirty-six days, but the collateral circulation was sufficiently competent to permit the return to a level which does not exceed the upper range of venous pressures for normal dogs.

PATHS OF COLLATERAL CIRCULATION

The paths of collateral circulation represent one continuous anastomosing system which, however, may be arbitrarily divided into several different groups. A distinction between superficial and deep collateral veins is of importance because the superficial collateral veins are of greater clinical interest.

OBSTRUCTION ABOVE THE AZYGOS VEIN

Superficial Veins.—Tributaries of the axillary vein, chiefly the thoraco-epigastric vein, join a plexus of superficial veins over the thorax and abdomen. Superficial veins of the neck anastomose with those of the thorax, but these collateral veins are not prominent in the dog. The return flow of blood from the superficial veins occurs largely through the intercostal veins. Communications with the superficial epigastric and superior and inferior epigastric veins permit a return of blood through the femoral and external iliac veins, but the path through the external iliac veins is not well developed when the obstruction is above the level of the azygos vein.

Deep Veins.—(*a*) The internal mammary vein, a tributary of the innominate vein, is an important vessel in the collateral circulation (fig. 1). Anastomoses with the intercostal, anterior mediastinal and superior epigastric veins permit the return flow of blood to the heart.

(*b*) The veins of the mediastinum form a prominent plexus composed of the anterior mediastinal veins, a group of posterior mediastinal veins and the pericardiac veins. Below they enter the superior phrenic veins, tributaries of the inferior vena cava.

(*c*) A group of veins along the vertebral column, especially the internal vertebral plexus, communicate, above, chiefly with the dural sinuses and the vertebral veins and, below, with the intervertebral and intercostal veins.

(*d*) There is a plexus of deep veins of the back formed chiefly by posterior rami of the intercostal veins. Descending branches of the transverse cervical and transverse scapular veins also appear to enter into the formation of this deep dorsal group.

(*e*) The lumbar, abdominal and suprarenal veins communicating with the superficial and deep veins of the back and with the abdominal wall empty into the inferior vena cava. The lumbar veins also join the azygos system through the ascending lumbar veins.

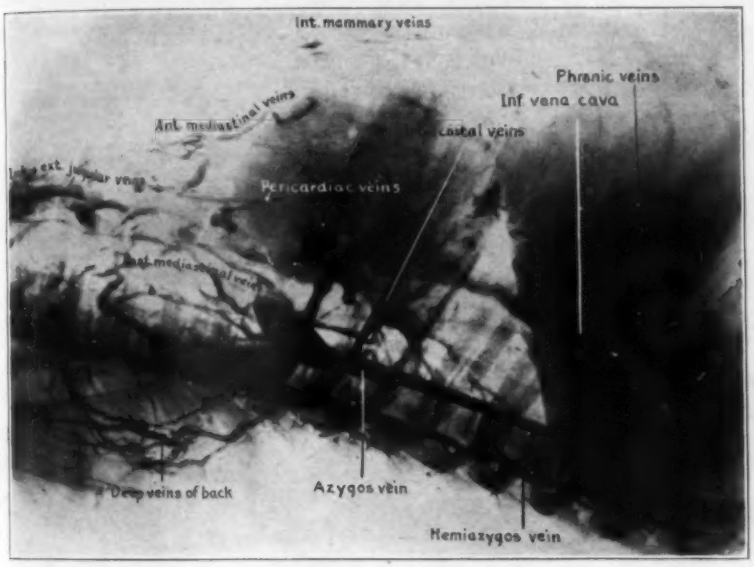

Fig. 1.—Injection of barium into the venous system to show collateral circulation after obstruction of the superior vena cava above the level of the azygos vein.

(*f*) The superior intercostal veins, other intercostal veins, and the accessory hemiazygos, hemiazygos and azygos veins form an important channel of collateral circulation.

In this type of obstruction (the superior vena cava being obstructed above the level of the azygos vein) the azygos vein with its tributaries becomes markedly distended and is the principal venous trunk through which blood returns to the heart from the upper part of the body.

COLLATERAL CIRCULATION AFTER OBSTRUCTION OF THE SUPERIOR VENA CAVA, INCLUDING THE AZYGOS VEIN

Superficial Veins.—The superficial veins are prominent over the chest and abdomen, beginning in the axilla chiefly with the thoracoepigastric veins and terminating below in the superficial epigastric tribu-

taries of the femoral veins. The superficial veins anastomose freely with the deeper veins (fig. 2).

Deep Veins.—(*a*) The internal mammary and the superior and inferior epigastric veins form a path from the innominate vein above to the external iliac vein below (fig. 3).

(*b*) The pericardiac veins and the anterior and posterior mediastinal veins form a well developed plexus of collateral veins traversing the mediastinal space.

(*c*) The vertebral venous plexuses are extensively developed, particularly the internal vertebral plexus, which may be traced clearly

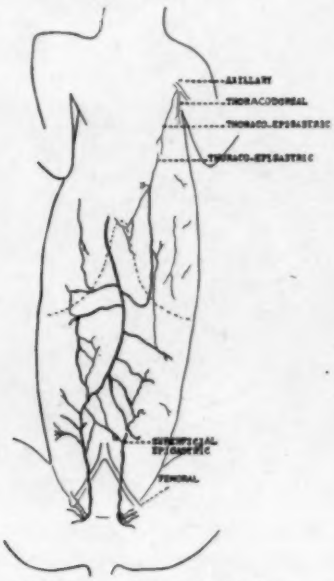

Fig. 2 (dog A-15).—A dissection of the superficial venous system after obstruction of the superior vena cava, including the azygos vein.

from the cervical to the lumbar region. The intervertebral, intercostal and lumbar veins anastomose with these plexuses.

(*d*) The deep collateral veins of the back are present, but are not prominent. They may be traced down to the lumbar region.

(*e*) The suprarenal, lumbar and abdominal veins of the dog communicate with the deep and superficial veins of the lumbar region and enter the inferior vena cava.

(*f*) The azygos system, being obstructed, is diminished in size, and the flow of blood through it is apparently reversed.

The differences between the paths of collateral circulation in the two types of obstruction may be summarized briefly. In the first type the azygos vein and its tributaries form the chief venous trunk for the

return flow of blood from the upper part of the body to the heart. The lower abdominal collateral veins are relatively unimportant. In the second type of obstruction the superficial and deep abdominal vessels and the vertebral plexuses are of much greater importance. As the azygos vein is blocked, all of the blood returns to the heart through the inferior vena cava.

In experimental studies of human cadavers, Wagner [2] found that the renal and the internal spermatic veins were important paths of collateral circulation, but they did not appear to be well developed in the experiments on dogs reported here.

Wagner also found that the superficial dorsal thoracic veins were more prominent when the obstruction was below than when it was

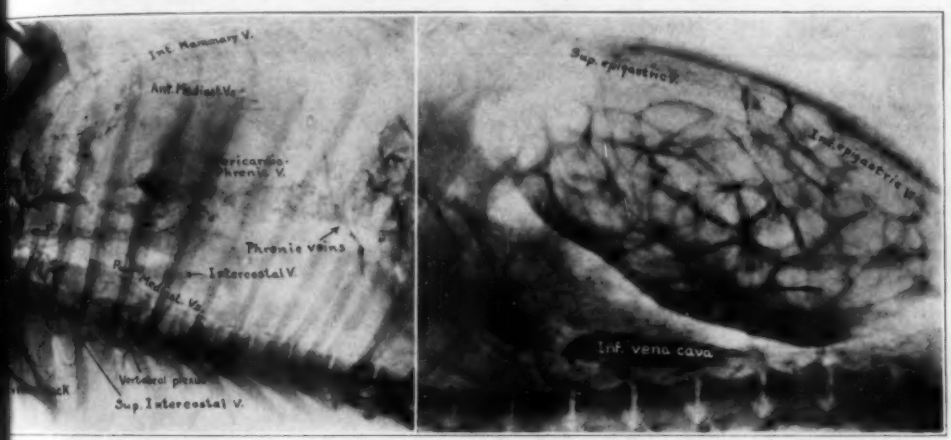

Fig. 3.—Injection of barium into the venous system to show collateral circulation after obstruction of the superior vena cava, including the azygos vein. The portal vein was apparently filled by back pressure. It did not prove to be a path of collateral circulation.

above the point of junction with the azygos vein. Dorsal superficial collateral veins were not well developed in the dog in either type of obstruction. No striking differences could be observed in the two types studied.

THE EFFECT ON ARTERIAL BLOOD PRESSURES

Carotid blood pressure tracings were taken on three dogs, the superior vena cava and the azygos vein being obstructed simultaneously through an open pneumothorax. In these experiments respiration was maintained by means of rhythmically interrupted positive pressure.

2. Wagner, K.: Symptomatology of Stenosis with Occlusion of Lumen of Superior Vena Cava, Polska gaz. lek. **11**:61 and 81, 1932; abstr., J. A. M. A. **98**:1342 (April 9) 1932.

Three experiments of this type showed that sudden total obstruction of the superior vena cava results in a drop of the arterial blood pressure to shock levels (fig. 4). Following the release of the obstruction a plethoric effect was noted, the blood pressure rising to a level higher than that preceding the obstruction, after which the blood pressure eventually became level again. The effect of prolonged obstruction was also noted (fig. 4). A sudden drop in arterial pressure occurred immediately after the superior vena cava was obstructed. From that time on there was a progressive drop in the pressure which, however, occurred slowly. The respirations became slow; after thirty minutes they were succeeded by gasping efforts. Finally all of the respiratory movements ceased, and respiration was entirely artificial. The heart action continued more than thirty minutes after the cessation of respiratory movements.

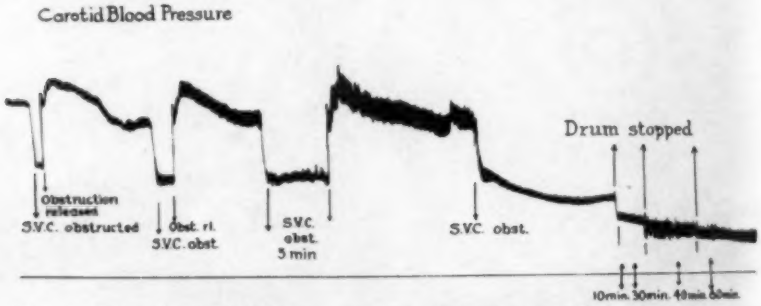

Fig. 4.—The effect of sudden, complete obstruction of the superior vena cava and azygos vein on the arterial blood pressure.

These changes in arterial blood pressure are probably not of much clinical significance, because the occlusion of the vessel usually occurs slowly in clinical cases. However, the rapid death of animals subjected to sudden total obstruction of the superior vena cava is apparently a result of the disturbed circulation of the respiratory center and other vital centers. This disturbed circulation consists of a fall in arterial blood pressure and a rise in venous pressure due to venous stasis. Changes in the oxygen and carbon dioxide tension of the blood were not investigated.

SUMMARY

Obstruction of the superior vena cava was produced above and below the azygos vein in such a way as to include the azygos vein. Dogs tolerate obstruction above the level of the azygos vein but not obstruction below the azygos vein when it is produced in one stage. Obstruction of the superior vena cava and the azygos vein may be produced successfully in two stages.

Marked cyanosis of the upper part of the body results from obstruction of the superior vena cava, but as collateral circulation develops, the cyanosis disappears. The collateral circulation eventually compensates for the obstruction, so that the animals appear healthy, and the venous pressures of the obstructed area become normal or are only slightly elevated. The paths of collateral circulation have been described.

The arterial blood pressure immediately after obstruction of the superior vena cava (including the azygos vein) drops to a shock level.

A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Stone.—Gayet [1] pointed out the difficulty encountered when lithiasis occurs in a solitary, infected kidney or bilaterally in kidneys with the renal parenchyma in an advanced stage of destruction. He reported 2 cases of this type in which minor operative procedures, such as incision of the renal parenchyma with insertion of an individual indwelling catheter and the opening of a perinephric abscess, had kept the patients from succumbing to the disease and had relieved them at least temporarily. In 1 case the right kidney was practically functionless whereas the left kidney contained a large stone. In the other case, the stone was in a horseshoe kidney; the urine was purulent, and there was a perinephric abscess communicating with the pelvis.

Most of the patients with these conditions are uremic and cannot endure a long operation under general anesthesia. The period of operation must be brief, and as a rule exteriorization of the kidney must be avoided as the organ may be acutely infected and may at times lie in the midst of a perinephric abscess. Fever and tension should first be reduced by nephrostomy; later, the calculi should be removed, so far as possible, through the opening made at nephrostomy by means of a finger, a blunt curet or fenestrated forceps. Only minor operative procedures may be performed in cases in which the kidneys are badly infected. Treatment should consist of such minor operative procedures repeated

1. Gayet, G.: Néphrolithotomies en plusieurs temps dans les cas graves de lithiase rénale, Bull. Soc. franç. d'urol., Jan. 15, 1934, p. 35.

as necessary; these procedures should be meticulously prepared for and followed by close surveillance afterward.

Nash [2] studied calculous pyonephrosis with a view toward clearing up some of the problems presented by this disease, especially toward bringing out the value of transperitoneal nephrectomy, devised recently to obviate the difficulties involved in secondary lumbar nephrectomy which is always required sooner or later after nephrotomy has been performed as a palliative measure. If a surgeon makes the mistake of performing a nephrectomy in one stage when the patient is run down, he is likely to lose that patient. Even in operations performed in two stages by the lumbar route there is still the danger of operating on a patient who is in poor condition and who has a kidney densely adherent to surrounding structures, nephrotomy not only having failed to eliminate the old adhesions but having also complicated the picture by removing the normal landmarks and creating new ones of scar tissue. Bleeding also complicates the situation and brings additional dangers.

Transperitoneal nephrectomy obviates these difficulties because the approach is through a fresh field. The abdomen is opened by a pararectal incision. The ureter, which is readily identified, is easily followed up to the pedicle, and the renal vessels can be ligated before any attempt is made to enucleate the kidney proper. Any adhesions present may be separated under vision without the disturbing element of uncontrollable bleeding.

In most cases of calculous pyonephrosis the patients are young women who have married at an early age and have gone through many and frequent pregnancies. It is suggested that urinary diathesis may predispose these women to an infection and to the formation of stone in the kidneys analogous to those in women with biliary diathesis in whom disease of the gallbladder originates at the time of their first pregnancy.

[COMPILERS' NOTE.—Although transperitoneal nephrectomy is best indicated for renal neoplasms, it should not be used systematically instead of typical lumbar nephrectomy because in most instances of calculous pyonephrosis in which the kidney has become greatly enlarged besides the shock of the operation there is the possibility that peritonitis may develop, and this, of course should always be avoided.

Gutierrez has stressed the value of lumbar nephrectomy in two stages, following preliminary drainage by nephrostomy, for highly debilitated patients for whom a hasty one-stage nephrectomy may have fatal results. It has been shown that these patients improve when the shock of the operation is thus divided, since they are able to build up

2. Nash, I. E.: Calculous Pyonephrosis: A Clinical Study with Special Reference to Etiology and Treatment; Review of the Literature, Report of Six Cases, Am. J. Surg. **24**:110 (April) 1934.

bodily resistance and to gain in renal function, resulting in cardiac compensation and in general detoxication. By this two step procedure a greater measure of safety is assured both to the patient and to the surgeon, and it is likewise obvious that it has served to reduce the mortality appreciably, particularly in cases of pyonephrosis in which the kidney has become considerably enlarged and in which nephrectomy by the lumbar route carried out extraperitoneally is correctly indicated.]

Quinby [3] stated that in the five years preceding 1931, 240 patients with renal or ureteral calculus were admitted to the Peter Bent Brigham Hospital. This period marks the beginning of his endeavor to adopt a consistent policy toward urinary stone, which was as follows: (1) to conserve renal tissue whenever possible by employing nephrectomy only when renal injury was great; (2) to consider the operation that removes a stone only the first event in the medical care of the patient, and to insist that whenever possible each patient return at suitable intervals for antiseptic treatment of the bladder and kidneys; (3) in cases in which operation is needed to persist until the roentgenogram taken at the operating table reveals that all the stones have been removed.

Of the 240 patients, 76 hospital patients and 45 private patients were available for the present analysis. A roentgenogram was taken of all the hospital patients when they returned; they received a general physical examination, and the urine was analyzed and cultured. Letters from the private patients or from their physicians were at times accepted instead of personal interviews.

One hundred and twenty-one patients were considered. One patient died at operation. Three other patients were not relieved and died later, giving a total mortality rate of 3.3 per cent. In 64 cases the stone or stones were situated in the kidney, and in 3 cases the stones were in both the ureter and the kidney. There were 6 cases of bilateral stones and 2 cases of unilateral stone. On the follow-up records of patients with renal stone, Quinby found that the stones had recurred in 21 cases (in 5 of the cases in which the stone was bilateral all the stones had not been removed at operation). Therefore, in 24, or 19.8 per cent of 121 cases, stones were still present. Further analysis has revealed that in nearly all the cases failure to relieve these patients permanently has been due to persistence of the original infection. It is clear, therefore, that, after a certain degree of renal injury has taken place, one is well-nigh powerless to conquer the coincident infection, even though persistent effort is made after the stone has been removed. Nephrectomy was performed in 24 cases as compared with 45 cases in which the calculus was removed by pyelotomy or by pyelonephrectomy. Although

3. Quinby, W. C.: End-Results of Operations for Lithiasis, Tr. Am. A. Genito-Urin. Surgeons **26**:285, 1933.

the majority of the patients who underwent nephrectomy were cured, the subsequent formation of multiple stones in the remaining kidney of 3 patients led to further operation and eventually to the death of 2.

Quinby stated that from all this study it appears that ureteral stones are likely to be associated with less infection and less injury to the kidney than stones which do not enter the ureter. This is doubtless largely due to the fact that urgent symptoms are caused by these relatively small stones at a much earlier date. Patients with renal calculi should be subjected to operation for the removal of such stones at an early date. It is a mistake to delay operation because the stone is causing no symptoms. The problem of urinary infection plays a large part in the incidence of formation of stone, and the end-result of the treatment of the stone depends considerably on the degree of such infection and on the physician's ability or inability to conquer it.

Tumor.—Simpson [4] considered the diagnosis, pathologic changes and treatment of carcinoma of the kidney. In his experience carcinoma of the kidney, in contradistinction to hypernephroma, papillary carcinoma of the renal pelvis and the embryonal adenosarcoma of children, gives rise to a syndrome characterized by: (1) severe pain in the back, which is constant, is unaffected by exercise and is caused by extension of the growth to the upper lumbar vertebrae; (2) hematuria, usually of short duration without recurrence, and (3) absence of any obvious enlargement of either kidney. Objective findings of unilateral reduction of function and collapse of one or more lumbar vertebrae complete the diagnosis. Following retrograde pyelography, the absence of pelvic deformity in early cases may be misleading. Even in advanced cases there may be little pelvic abnormality. Simpson considered involvement of the upper lumbar vertebrae to be the result of local extension through lymphatic structures rather than of metastasis, and in support of this contention he quoted the report of a case of Fraser's in which only half of the body of the first lumbar vertebrae was involved on the side of the affected kidney.

In contrast to other renal tumors carcinoma infiltrates and replaces renal tissue without perceptible enlargement, so that clinically there is no palpable tumor.

Four cases are reported, in all of which these characteristic symptoms were present.

Kimball and Ferris [5] stated that the pelvis of the kidney is involved by neoplasms much less commonly than the renal parenchyma. In 1924,

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4. Simpson, Graham: Carcinoma of the Kidney, Brit. J. Surg. **21**:388 (Jan.) 1934.

5. Kimball, F. N., and Ferris, H. W.: Papillomatous Tumor of the Renal Pelvis Associated with Similar Tumors of the Ureter and Bladder; Review of Literature and Report of Two Cases, J. Urol. **31**:257 (March) 1934.

Thomas and Regnier reviewed 248 cases in which tumors invaded the renal pelvis, ureter and bladder; they found that the renal pelvis alone was involved in 33 per cent, the renal pelvis and ureter in 14 per cent, and the renal pelvis, ureter and bladder in 8 per cent of the cases. Papillary tumors of the renal pelvis grow slowly and cause profuse hematuria. This hematuria, often massive and sometimes painless, is the most predominant symptom; it occurred in 96 per cent of 74 cases studied by Kimball and Ferris. It occurs comparatively early in the course of this condition. The longest duration recorded was of intermittent hematuria over a period of twenty years. Pain was usually caused by secondary obstruction resulting from intermittent and variable hydronephrosis. It was accompanied by hematuria in 52 per cent of the cases. In only 15 per cent could a mass be felt and, when a mass was palpable, it was usually cystic and soft, and was caused by hydronephrosis.

Kimball and Ferris stated that cystoscopic data are extremely significant in cases of tumor of the renal pelvis. It was the means of diagnosis in 85 per cent of the cases studied. The growth usually originates in the wall of the renal pelvis and occasionally invades the parenchyma. The tumor may vary from a small, localized tuft to an extensive mass that completely fills and distends the pelvis. The metastatic growths in the bladder may be either single or multiple, and they usually are near the affected ureteral orifice. The ureteral orifices and adjacent bladder were involved in 48 per cent of the cases of Kimball and Ferris. At the time the reports of the cases were published there were known recurrences in 64 per cent of the cases and no known recurrences in 32 per cent after removal of the primary tumor. The original tumor was malignant in 38 cases, or 51 per cent, and benign in 36 cases, or 49 per cent. In the group in which the original tumor was malignant the recurrences were malignant in 75 per cent and benign in 20 per cent of the cases.

Kimball and Ferris stated that tumors of the renal pelvis are inherently malignant and that the microscopic characteristics of benignancy do not insure innocent behavior on the part of the tumor. Recurrences in the lower segments of the ureter and in the bladder have often been observed. In Kimball and Ferris' series of 74 collected cases, 40 patients were treated by nephrectomy and 25 by nephro-ureterectomy, including the intramural part of the ureter. Thirty, or 75 per cent of the 40 patients who underwent nephrectomy, are known to have had recurrences. Secondary ureterectomy was performed on 21 of these patients, with further recurrences in 12, or 57 per cent. The known mortality in the group treated by nephrectomy was 33 per cent. Primary nephro-ureterectomy, without including the intramural part of the ureter, was performed in 25 cases. There were known recurrences in 17, or

68 per cent, of these cases. Further resection of the intramural part of the ureter was done in 12 cases, with still further recurrences in 4 cases. The known mortality for this group was 44 per cent. In only 6 cases was primary nephro-ureterectomy, which included the intramural part of the ureter, performed. In 2 of these cases the diagnosis was benign tumor and in 4, malignant tumor. The known mortality in the group of cases of malignant tumor was 25 per cent. Of the total of 74 patients, 28 were known to have died, a mortality of 38 per cent.

Kimball and Ferris state their belief that in the treatment of papillomatous tumors of the renal pelvis, nothing short of primary, complete nephro-ureterectomy, with resection of the intramural part of the ureter should be considered.

Hydronephrosis.—Fagge [6] presented a case of advanced hydronephrosis of the right kidney, in which the symptoms were referable chiefly to the gastro-intestinal tract. For years the patient had had indigestion, with attacks of pain, nausea and vomiting, suggestive of an intermittent duodenal obstruction. These attacks had been brought on and relieved by a change of posture.

A study of the gastro-intestinal tract revealed compression, marked elongation and mesial displacement of the second portion of the duodenum. There was no palpable mass, but an excretory urogram revealed advanced hydronephrosis of the right kidney with a large extrarenal pelvis displacing the duodenum. Removal of the kidney completely relieved the gastro-intestinal symptoms.

[COMPILERS' NOTE.—Silent hydronephrosis is not uncommon. There may be advanced hydronephrotic atrophy without any symptoms referable to the urinary tract. This is especially true of hydronephrosis of the left kidney. When the right kidney is involved, however, and especially when there is large extrarenal pelvic dilatation because of its relation to the second portion of the duodenum, the symptoms may be predominantly or entirely gastro-intestinal, with a syndrome characteristic of gastroduodenomesenteric ileus or intermittent duodenal obstruction.

During an attack relief may be obtained by changes in posture; the extreme Trendelenburg position usually gives relief.]

Hinman,[7] in an experimental study of hydronephrosis, has thrown light not only on the mechanism of this condition but also on the causes of many other renal disturbances. Complete obstruction of the excretory ducts of other glands (salivary, pancreatic and biliary) produces primary

6. Fagge, C. H.: Case of Hydronephrosis, Brit. J. Surg. **21**:151 (July) 1933.

7. Hinman, Frank: Pathogenesis of Hydronephrosis, Surg., Gynec. & Obst. **57**:356 (Feb.) 1934.

atrophy and necrosis, but complete obstruction of the ureter results in a condition that is unique, namely, progressive hydronephrotic atrophy. Primary atrophy occasionally occurs, and the secondary changes vary, giving the picture of a secondarily contracted kidney, of the changes caused by infection or of attempts at repair.

The results of the experimental work of Hinman are summarized under five headings: (1) pathologic changes produced by ureteral obstruction; (2) effect of prolonged modification of secretory pressure on the rate of the production of these changes; (3) effect of relief of obstruction on these changes; (4) relation of structure to these changes, exemplified by the comparative variations in living forms, and (5) relation of renal hydromechanics to the production of hydronephrosis and primary atrophy.

1. The pathologic changes produced by complete ureteral obstruction in the unipapillary kidneys of the rabbit or dog are characterized by progressive pelvic distention and by parenchymal atrophy. The pathologic changes of hydronephrosis in the metanephros of the rabbit are characterized by progressive ureteropelvic distention and by parenchymal atrophy. The tubules undergo dilatation, collapse and atrophy. The glomeruli persist longest. The changes are found in groups of structures and are not diffuse and uniform. This early atrophy of certain groups and the relative preservation of others are related to the blood supply. Both pelvic and tubular distention affect the renal circulation. Back pressure is the primary and essential factor, but anemic atrophy is the more active and controlling factor in producing the changes of hydronephrotic atrophy.

2. The effect of prolonged modification of secretory pressure (intrapelvic pressure) on the rate of development of hydronephrosis was studied by producing polyuria and oliguria, by lowering secretory pressure through prolonged partial constriction of the renal artery and by raising secretory pressure through prolonged partial constriction of the renal vein. It might be assumed that variations in intrapelvic back pressure would cause proportionate variations in the rate of development of hydronephrotic atrophy. It was found, however, that experimentally this was not so, and that polyuria or oliguria in no way modified the rate of progressive dilatation. The slightest modification of the blood supply producing parenchymal anemia hastened the dilatation to a marked degree, even when the intrapelvic pressure was lowered at the same time; this indicated that although increased intrapelvic pressure is essential to hydronephrotic atrophy, the rate of development is largely determined by the secondary circulatory changes with the resultant anemic atrophy.

3. The effect of the removal of the ureteral obstruction on hydronephrotic atrophy was studied by ligating and dividing one ureter near

the bladder, so that later the obstruction could be relieved and the ureter transplanted into the bladder. Modifications of the rate of repair were studied by varying the stimulus or demand for repair by operations on the opposite normal kidney, that is, by nephrectomy at varying periods or by slow destruction of the kidney through partial obstruction of its ureter. It was found that the repair of hydronephrotic atrophy, following removal of the obstruction of the ureter, is characterized grossly by shrinkage in size and microscopically by the return of the less injured groups of glomerulotubular units to a more normal appearance. The glomerular and convoluted portions of the units in which repair has taken place show hypertrophic changes. Restoration of function is proportional not only to the number of structural units in which repair takes place but also to the degree of hypertrophy in each. With repair the same stage of hydronephrotic destruction shows, in different kidneys, a variation in the degree of these hypertrophic changes according to the nature of the excretory burden placed on the kidney at the time the obstruction in the ureter is removed. The maximal amount of repair of structure and restoration of function follows a gradual shifting of the burden, such as follows slow destruction of the opposite kidney.

4. The question arises whether hydronephrotic atrophy is peculiar to or dependent on the structural arrangements as seen in mammals in which the kidneys are metanephric, either unipapillary without columns of Bertin or multipapillary with such columns. The arrangement of the pelvis to the blood supply is intimate. All other kidneys are without a pelvis, and the blood vessels enter on the side opposite the excretory duct. The question arises: Can hydronephrosis develop with this structural arrangement? It was found that the pathologic changes of hydronephrosis occur only in kidneys which have internal glomeruli. The gross and microscopic changes occur most typically in the mammalian kidney, which has a hilus and a pelvis. This structural arrangement, however, is not essential. Similar changes follow complete obstruction of the ureter or of the primary excretory duct of the apelvic kidneys of reptiles, birds and amphibians. The microscopic changes which follow the direct obstruction of tubules in the pelvic type of kidney, such as occurs when a papilla has been tied, resemble those which follow indirect obstruction, such as occurs when the ureter has been tied.

5. The development of hydronephrosis presupposes the continuation of renal activity with the maintenance of intrapelvic pressure. This can take place only if there is resorption. There has to be an inflow and outflow, and this can take place only through resorption when the ureter is completely blocked. This theoretical assumption is confirmed by experimental observations. The mechanical factor in the development of hydronephrotic atrophy is a backflow of urine into the venous

system. In mammalian kidneys this backflow is probably at first pyelovenous and later becomes tubulovenous. In the apelvic mesometanephros of the reptile, bird and amphibian the backflow fails to occur on complete obstruction of the excretory duct; anuria develops, and the pathologic change of primary atrophy, instead of hydronephrotic atrophy, results.

Mathé and de la Peña [8] stated that a high percentage of failures has been reported by surgeons who, having previously performed plastic operations on the kidney for hydronephrosis, have checked their results after operation by the ureteral catheter, by studies of renal function and by pyelography. These failures are due to the following factors: improper or insufficient correction of the obstructing lesion in the upper part of the ureter and ureteropelvic juncture, improper selection of the particular type of plastic repair for each individual case and lack of appreciation of certain technical points that are necessary for permanent relief of renal retention and hydronephrosis. The most common causes of failure in correcting etiologic obstructive lesions are: buckling of the mucosa following the Fenger operation of longitudinal incision and transverse closure for stricture and valve formation of the ureteropelvic juncture, lack of proper disposition of obstructing, anomalous vessels, neglect to perform thorough ureterolysis and failure to employ nephropexy.

The most common causes of hydronephrosis in the upper part of the ureter are: (1) movable kidney, with angulation of the ureter over anomalous blood vessels, angulation over fibrous bands in the perirenal tissues and angulation due to the collapse and adhesion of the ureter against the side of the pelvis; (2) lateral insertion of the ureter; (3) inflammatory contracture or stricture of the ureteropelvic juncture; (4) formation of calculi in the upper part of the ureter and pelvis, and (5) sclerosing, infectious and traumatic perinephritis. Patients with early hydronephrosis secondary to a movable kidney associated with angulation of the ureter, in whom the angulation is due to fibrous bands or to a collapse of the ureter and adhesion to the pelvic wall, can usually be relieved by ureterolysis and by nephropexy. Hydronephrosis secondary to smaller aberrant vessels is best relieved by ureterolysis, resection of the vessels and nephropexy. In cases of early hydronephrosis caused by a stricture of the ureter of large caliber and formation of valves at the ureteropelvic juncture, relief can be obtained by longitudinal incision with transverse closure. In advanced cases of formation of a stricture, resection of the sclerotic ureteropelvic juncture, reimplantation of the ureter into the pelvis and temporary nephrostomy

8. Mathé, C. P., and de la Peña, Emilio: Surgical Repair of Hydronephrosis, with Reference to Technical Points Favoring Relief, J. Urol. **31**:1 (Jan.) 1934.

are indicated. In hydronephrosis due to sclerosing, infectious and traumatic perinephritis, nephrolysis and ureterolysis should be performed, and the type of repair which is based on the nature and extent of the hydronephrotic sac should be utilized.

Single Kidney in Pregnancy.—Prather and Crabtree [9] stated that, in general, nephrectomy is not a contraindication to pregnancy. They reported the cases of 296 women who had undergone nephrectomy, 365 pregnancies having subsequently developed among these women. In 55 per cent of these cases nephrectomy had been performed because of tuberculosis. Renal pelves and the upper part of the ureters undergo the familiar type of dilatation encountered during pregnancy. The right kidney reveals a greater degree of dilatation than the left kidney. If the kidney is normal tests of renal function reveal an adequate margin of safety during pregnancy. The study of these patients should include thorough physical examination, repeated examinations of catheterized specimens of urine, inoculation of guinea-pigs with specimens of urine from patients who give a history of tuberculosis of the urinary tract, studies of the blood, two hour tests with phenolsulphonphthalein and intravenous pyelography.

Many early investigators advised against marriage for the woman who had undergone nephrectomy. Accumulated statistics indicate a mortality rate of from only 1.09 to 1.4 per cent. In patients who on examination are not found to have any abnormalities pregnancy should always be allowed to continue, though under close observation. Prather and Crabtree believed that the desire to avoid permanent renal injury, combined with closer study, may in the future result in a somewhat higher percentage of interruptions of pregnancy; the indications for such interruptions are: the finding of an injured kidney early in pregnancy and obstetric or renal complications later.

Supernumerary Kidney.—Saccone and Hendler [10] reported the accidental finding of a supernumerary kidney at necropsy. There was no communication between the two kidneys, which were on the left side; each had a separate supply of blood and a separate ureter, the ureters fusing below the pelvic brim and outside of the bladder. In this case the supernumerary kidney had been a normal, functioning, independent organ, as was revealed by its anatomic position and by microscopic study. Symptoms referable to the genito-urinary tract had never been noted. The total number of such cases reported, including this one, is 36.

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9. Prather, G. C., and Crabtree, E. G.: The Lone Kidney in Pregnancy, Tr. Am. A. Genito-Urin. Surgeons **26**:313, 1933.

10. Saccone, Andrea, and Hendler, H. B.: Supernumerary Kidney: Report of a Case and Review of the Literature, J. Urol. **31**:711 (May) 1934.

Heminephrectomy.—Campbell [11] reported 5 cases of hemipyonephrosis among young children. Double kidneys are more prone to disease than normal organs. This lesion may cause persistent urinary infection among juveniles and, because of pyuria, the diagnosis of chronic pyelitis is commonly made. Complete urologic examination is essential to the correct diagnosis of hemipyonephrosis. Ureteroheminephrectomy is the treatment of choice when half of the double kidney remains undiseased, and the operation is technically feasible if the condition of the patient permits. If marked renal infection is present, especially if it is acute, nephrectomy is often the best procedure. Ureteroheminephrectomy was successfully performed in the case of an infant 6 months of age, the youngest patient in this series.

Perinephric Abscess.—Kessler, Bennetts and Bacon [12] stated that pathologic processes that present practically all the signs and symptoms of perinephric abscess may lie entirely outside the renal fossa. When surgical exploration for perinephric abscess is unsuccessful, there should be careful consideration and diagnostic investigation of all the structures adjacent to the kidney. In this region suppuration of structures other than the kidney and perinephric fat have the same etiologic background, that is, hematogenous infection from foci of suppuration elsewhere, and such conditions occur with sufficient frequency to warrant their consideration in cases of suspected perinephric abscess.

Polycystic Disease.—Walters and Braasch [13] stated that the contention that surgical treatment of polycystic kidney is seldom if ever indicated, is erroneous. Complications with polycystic kidney that require surgical treatment occur frequently. The estimation of renal function is of fundamental importance in determining the prognosis and advisability of operation. Owing to anatomic conditions present in the polycystic kidney, retention tests of renal function usually give a better index than excretory tests. Evidence of marked disturbance of function in both kidneys, such as is indicated by a value for urea of from 50 to 60 mg. or more per hundred cubic centimeters of blood, is usually a contraindication for surgical treatment except as an emergency measure. When complications indicating nephrectomy are present in one kidney it is essential to determine first whether the degree of function of the other kidney is sufficient to sustain life. Bilateral renal deformity, visualized by intravenous or by excretory urography,

11. Campbell, M. F.: Hemipyonephrosis in Infants and Children, Am. J. Surg. **21**:85 (July) 1933.

12. Kessler, E. E.; Bennetts, F. A., and Bacon, S. K.: Perinephritic Abscess, Am. J. Surg. **22**:223 (Nov.) 1933.

13. Walters, Waltman, and Braasch, W. F.: Surgical Aspects of Polycystic Kidney, Tr. Am. A. Genito-Urin. Surgeons **26**:385, 1933.

should serve to make evident the comparative degree of function in either kidney and to govern the type of operation and its advisability. A polycystic kidney has not infrequently been removed after a clinical diagnosis of renal tumor.

The most common complication occurring with a polycystic kidney and requiring surgical treatment is diffuse or localized infection. Diffuse, subacute renal infection may have an insidious onset, and there may be but few localizing symptoms. Renal pain is a common symptom and is usually described as a dull ache, although it may become acute. It may be caused by excessive renal weight, exerting a pull on the renal pedicle, by intracystic or external pressure or by infection. Puncture or enucleation of one or more large cysts may serve to ameliorate the condition or to eradicate pain. Hematuria, usually of moderate degree and of limited duration, may become copious and long continued. Such hematuria is usually the result of intracystic hemorrhage, with rupture of the cyst into the renal pelvis. Excision or enucleation of such cysts usually suffices to control the hemorrhage. Should destruction of the kidney be extensive accompanied by secondary infection, nephrectomy may be necessary. Other complications observed with polycystic kidney are renal calculus, neoplasm, tuberculosis and hydronephrosis.

Nephrostomy.—Cabot [14] stated that, as a rule, reimplantation of the ureter into the bladder is not mechanically feasible. The results are by no means satisfactory, and pyonephrosis, at least, commonly results. This raises the question of implantation of these injured ureters into the bowel. Transplantation of a ureter made abnormal as the result of obstruction is, however, attended by a risk considerably greater than that attending the transplantation of a normal ureter. This increased operative risk has seriously interfered with surgeons' willingness to undertake the operation.

In the last two years Cabot has been interested in studying the possibility that preliminary nephrostomy, resulting in adequate drainage of the kidney, would eliminate the additional risk and make transplantation of these ureters a sound undertaking. His experience with 3 such cases, in 1 of which bilateral nephrostomy and bilateral ureteral transplantation were performed (3 patients and 4 ureters), is encouraging. Nephrostomy has had the effect of maintaining the function of the kidney and of apparently improving it; transplantation, carried out after an interval of several weeks, has proved simple and satisfactory. It has been notable that the technic of the operation has been easy; wounds have healed nicely, and there has been a notable absence of

14. Cabot, Hugh: Nephrostomy Preliminary to Transplantation in Cases of Injury to the Ureter, Proc. Staff Meet., Mayo Clin. **9**:125 (Feb. 28) 1934.

fever postoperatively. Drainage has been continued for about two weeks after transplantation, and then, on removal of the tube, the ureter has gone into action without incident and with prompt closure of the wound. In fact it has been surprising that the wounds made at nephrostomy have not leaked after the first twenty-four hours following removal of the tube.

Cabot presented in some detail a case in which bilateral nephrostomy had been performed; both ureters had been transplanted, at separate times. This case, coupled with the 2 in which the procedure was of shorter duration, suggests that under these conditions nephrostomy as a preliminary to ureteral transplantation can be performed with a low immediate mortality rate and with at least as good probability of maintaining the integrity of the kidney as by any other method. It also suggests that preliminary nephrostomy diminishes the risk of transplanting the ureter.

Gutierrez [15] has called attention to the desirability of performing carefully planned nephrectomy in two stages in cases of advanced pyonephrosis in which the patient is too ill to be subjected to primary nephrectomy, especially when a perinephric abscess is present or when tuberculosis or calculous pyonephrosis is accompanied by an enormous enlargement of the kidney and by grave, toxic symptoms. The same principle should be followed in renal as in general surgery. Drainage of a pyonephrotic kidney to relieve the gravity of the symptoms before a radical operation is undertaken is a logical procedure, and it may be the means of saving the life of the patient.

The most important indications for this combined procedure are observed in anuria caused by calculus, in infected hydronephrosis, in pyonephrosis with perinephric abscess, in hydro-ureteropyonephrosis with or without calculus, in tuberculous pyonephrosis, in certain types of nephrolithiasis and in surgical nephritis. It is also indicated after nephrolithotomy or after pyelotomy for the removal of calculi and for derivation of the urine when the ureter is incapacitated, as well as in certain types of congenital malformations, such as horseshoe kidney with bilateral hydronephrosis, pyonephrosis or nephrolithiasis. It has its widest application when its primary purpose is the relief of urinary symptoms arising from retention and infection. The most important point lies in minimizing the surgical shock produced by the removal of extensive pyonephrosis, thus enabling the patient to build up bodily resistance by a course of general detoxication, strengthening of the cardiac and renal function and relieving of septic symptoms, chills, fever, acute urinary disturbance and general autointoxication.

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15. Gutierrez, Robert: Nephrostomy as a Preliminary Drainage in Preparation for Secondary Nephrectomy, J. Urol. **31**:305 (March) 1934.

Secondary nephrectomy is not always easy to perform owing to the presence of long-standing adhesions, but with a correct preoperative diagnosis it can be performed without danger. It should be performed as soon as the patient's general condition permits. Nearly every secondary nephrectomy becomes a subcapsular procedure, owing to the difficulty of exposing the kidney and of controlling the bleeding in some cases. In subcapsular nephrectomy as much as possible of the fatty capsule should be removed to prevent suppuration and to aid in healing of the wound.

Livermore [16] stated that the benefit from nephrostomy does not seem to be appreciated by the profession. Although Cabot and Holland and Boyd and others have reported how satisfactorily it has served them, it is not being used as often as its worth demands. Because of his appreciation of the value of nephrostomy, Livermore has presented his experience. Some years ago he performed nephrostomy to induce diuresis in anuria caused by poisoning with corrosive mercuric chloride. This consisted of rapid decapsulation and nephrostomy; the incision was made parallel and just posterior to the convex border of the kidney, and gauze saturated with 10 per cent solution of sulphonated bitumen in glycerin was packed through the wound into the renal pelvis. Although the two patients on whom the operation was performed died, the procedure proved its worth in establishing excretion of urine, which excretion continued up to the time of death.

The main indications for nephrostomy, as given by Cabot and Holland, are the presence of obstruction which cannot be satisfactorily remedied by some other method, namely: (1) acute obstruction, either of both ureters or of the remaining ureter, as in anuria caused by calculus or in malignant disease obstructing the ureter; (2) hydronephrosis, or infected hydronephrosis, in which the cause of obstruction may be removable but in which drainage of the kidney as a temporary measure is indicated to improve function; (3) renal calculi with badly injured kidneys; (4) carcinoma of the bladder in cases in which cystectomy is occasionally thought suitable; (5) failure of the musculature of the pelvis, ureters and bladder to evacuate urine, and (6) renal infection without high grade obstruction, in which case nephrostomy is performed to avoid renal infection and to allow recovery.

Livermore reported that in his cases the indications for nephrostomy had been: anuria from the acute nephritis of mercurial poisoning (3 cases); anuria due to stricture of the ureter (1 case); failing renal function from obstruction of the ureter due to ureteral calculi (2 cases),

16. Livermore, G. R.: Nephrostomy, Tr. Am. A. Genito-Urin. Surgeons **26**: 367, 1933; discussion on Gutierrez.[15]

and infected hydronephrosis in one functioning kidney due to kinking of the ureter (1 case). The technic employed was as follows: The kidney was exposed and freed if possible. The method of Cabot, namely, opening the pelvis and passing a U-shaped sound into this opening and out through the cortex at a point that satisfactorily drains the lower calix, is excellent; when the kidney cannot be freed, however, an opening may be made in the convex border or on the posterior surface of the kidney, and the pelvis entered. Livermore stated that he had not used the winged catheter advocated by Cabot but had relied on a number 22 to 35 French catheter, cutting off its tip so as to have an opening in the end. The catheter may be retained in the pelvis by suture to the capsule of the kidney with number 2 plain catgut sutures and anchored to the skin by two sutures of silkworm gut. When the sinus has been well formed a new tube may easily be inserted and held in place by strips of adhesive tape through a safety-pin in the tube. All these patients have symptoms of uremia, and most of them are very anemic. All measures for the promotion of diuresis must therefore be instituted. Transfusion of whole blood not only improves the patient's general condition but also increases the renal function.

Livermore stated that nephrostomy preliminary to secondary nephrectomy should prove of value in selected cases as it is often a life-saving procedure. In the anuria caused by obstructions of the ureter, either bilateral or in the ureter of a single kidney, which cannot be relieved, and in the anuria of acute poisoning by corrosive mercuric chloride, or when the condition of the patient precludes any lengthy operation, nephrostomy can be quickly performed. It is not necessary to free the kidney; exposure of the posterior surface or of the convex border makes it possible to incise the kidney and to pass a tube into its pelvis. The tube should be anchored to the capsule of the kidney with plain number 1 catgut and to the skin with silkworm gut. In some cases it is not unusual to note urine dripping from the tube before the patient leaves the operating room; patients in whom this occurs are particularly benefited by nephrostomy.

Obstructing and Inflammatory Lesions.—Walters [17] stated that emergency operations on the kidneys and ureters are usually performed because of obstructing lesions interfering with the adequate passage of urine. The association of renal infections with obstruction produces symptoms characteristic of toxemia, the result of pyelovenous backflow or of absorption of toxins and bacteria from severe cortical infections, usually with abscesses. Striking examples of restoration of renal

17. Walters, Waltman: Acute Obstructing and Inflammatory Lesions of the Kidneys and the Ureters, Ann. Surg. **98**:789 (Oct.) 1933.

function after the removal of renal and ureteral calculi and complete drainage of the kidney by temporary nephrostomy are convincing arguments in favor of using such conservative methods of caring for the lesions rather than resorting to treatment by nephrectomy. This is true in most cases even when there is considerable infection within the renal pelvis (infected hydronephrotic sac) and, occasionally, within the renal parenchyma. If a kidney is producing general evidence of severe infection and toxemia, however, and the opposite kidney is normal, immediate removal of the affected kidney is usually essential to recovery of the patient.

Walters stated that one normally functioning kidney will maintain adequate renal function in the presence of complete obstruction of the other kidney; thus, any evidence of renal insufficiency in such cases indicates that the function of the other kidney is not adequate. There are a few exceptions to the rule, but when there is doubt, nephrostomy rather than nephrectomy is the advisable procedure.

Walters stated further that perinephric abscess is characterized by a typical clinical picture consisting of pain in either renal area, fever, leukocytosis, tenderness to pressure and in most cases scoliosis with obliteration of the line of the iliopsoas muscle evident on roentgenologic examination. In such cases surgical exploration of the perirenal region is always advisable. Intrarenal hemorrhage that requires emergency surgical procedures is rare, but it may develop in cases in which there is traumatic fracture of the kidney or of its vessels or, although rarely, following operation on the kidney.

Braasch [18] noted that adequate drainage can frequently be established by means of the ureteral catheter. Nephrostomy or pyelostomy also gives the desired drainage. If an acute cortical infection is present, however, neither drainage by catheter nor nephrostomy will correct the condition, and immediate nephrectomy is advisable. If on exploration many small abscesses are found scattered over the entire kidney and if the other kidney is similarly affected the question whether nephrectomy would be advisable may well be asked.

The clinical diagnosis of cortical infection may be difficult. Often the evidence of toxemia is the best guide. The patient has a toxic appearance and complains of headache and stupor. There may be no localized tenderness or pain in the region of the affected kidney. In doubtful cases it would be a conservative procedure to remove the kidney in order to prevent the possibility of secondary infection of the other kidney by way of the blood stream. This course would be preferable to waiting until the other kidney becomes involved, a condition which

18. Braasch, W. F., in discussion on Walters.[17]

would be shown by an increase in the blood urea. At necropsy, cortical infection is usually found in the other kidney, and often such an infection would not have developed if the primarily infected kidney had been removed earlier.

Braasch mentioned another phase of the problem, brought out by Walters in demonstrating how dependent one is on intravenous or excretory urography. For various reasons the general surgeon has been slow to adopt this most valuable adjunct in the diagnosis of renal conditions. One reason may be that he regards urography as being within the exclusive province of the urologist. Braasch does not think that it is. Intravenous urography is a method of general diagnosis, and it should be employed more often, as it undoubtedly will in the future. The only difficulty is the matter of interpretation; with increasing familiarity with interpretation of the intravenous urogram, however, the method will be employed in routine differential diagnosis of abdominal disease. More and more diagnoses are being made by the country practitioner by means of this invaluable method. It has proved of great value in the evaluation of postoperative results. Braasch warned, however, that one should not expect too much from intravenous urograms made within a week or ten days after operation on the kidneys. A reflex inhibition of excretion often persists for several weeks. If urograms are taken two weeks or a month later most interesting data which could be acquired in no other way are often available.

Intravenous or excretory urography is of great value to the surgeon in interpreting roentgenographic shadows, in determining the position of the stone in the kidney and in ascertaining the function of both kidneys. Next in importance is the aid it gives in the demonstration and visualization of stasis; in this respect it is unquestionably of great value to general practitioners. It is also of great value in injuries of the kidney. From the evidence of extravasation of urine into the surrounding tissues it is possible to determine not only when rupture of the kidney is present, but also its degree. Rupture of the bladder is much better demonstrated by means of the intravenous cystogram than in any other way. Thus the danger of ascending infection from catheterization is avoided.

Beer [19] stated that it is well known that a stone in the ureter may inhibit renal function. A catheter passed up to the stone may fail to collect a specimen of urine and give the impression that the kidney is definitely not functioning; as a matter of fact, in many of these cases an intravenous urogram may show that there is no function. Not knowing this, the general surgeon may operate on the kidney to inspect

19. Beer, E., in discussion on Walters.[17]

it, and perhaps remove it. Beer believed that the rational procedure in cases of so-called "resting kidney," or "hibernating kidney," was to remove the obstructing stone. He did not believe that the kidneys were resting or hibernating; on the contrary he believed that they were secreting all the time, although one could not collect a specimen. He said that in every abdominal condition in which the diagnosis is not clearcut, a flat plate roentgenogram, an intravenous urogram and a series of tests of the gallbladder and of the gastro-intestinal tract should be made.

Typhoid Infection.—Huggins and Roome [20] reported 2 cases in which the patients were carriers of chronic urinary typhoid infection and had pyonephrosis with calculi. In both cases a cure was obtained by excision of the pyonephrotic kidney. The importance of a complete urologic examination of these carriers is emphasized.

URETER

Tumors.—Colston [21] reported a case of primary papillary epithelioma of the ureter in which existed the hitherto unreported complication of implantation of the tumor in what probably was a preexisting diverticulum of the bladder. The treatment consisted primarily of nephrectomy, which was followed by complete ureterectomy nine months later when the correct diagnosis was made. Six months after the second operation the diverticulum containing the implant was removed. The correct diagnosis was not made until persistent bleeding from the ureter was discovered on cystoscopic examination and the ureterogram presented a typical picture. Colston also reported 2 other cases from the records of the Brady Urological Institute, in both of which the patients died.

The value of the diagnostic syndrome of Chevassu and Mock, obstruction to the passage of a ureteral catheter followed by a copious flow of blood from the ureteral orifice, and the great importance of the ureterogram are emphasized. Complete nephro-ureterectomy is the method of choice, and all observers who have written on the subject say that it should be employed in all the cases in which the condition of the patient permits. The inadequacy of many methods of so-called complete nephro-ureterectomy is emphasized, as the mucous membrane of the distal stump of the ureter is not removed or destroyed by those methods. The extreme importance of complete eradication or destruction of the ureteral mucous membrane, especially in the intramural portion of the ureter where implantation of a tumor has been shown to

20. Huggins, C. B., and Roome, N. W.: Typhoid Pyonephrosis: Its Urological and Public Health Significance, J. Urol. **31**:587 (April) 1934.

21. Colston, J. A. C.: Primary Tumors of the Ureter, Tr. Am. A. Genito-Urin. Surgeons **26**:65, 1933.

occur, is emphasized. A method of complete ureteronephrectomy is reported, combining the previously well known steps but adding the hitherto unreported technic by which the mucous membrane of the distal stump of the ureter is completely destroyed by high frequency current throughout its course through the wall of the bladder.

Anastomosis.—Higgins [22] presented a technic for simultaneous bilateral transplantation of the ureters into the rectosigmoid colon. In his method the continuity of the ureter is not interrupted until the new channel develops, and the normal physiologic function of the upper part of the urinary tract is not altered until the anastomosis has formed. The simplicity of the procedure allows the operation to be performed on a child with exstrophy of the bladder, before the development of renal complications. Higgins reported a case in which a boy, aged 4 years, underwent such an operation and in which a most satisfactory result was obtained with only a slight postoperative reaction. Examinations of the kidneys and ureters of dogs have been made six months after this operation, and evidence of hydronephrosis or of infection has not been observed. Higgins stated that experience with animals has shown that following this procedure peritonitis, shock and acute renal sepsis are reduced to a minimum.

Injury.—Stevens [23] stated that injury to the ureter is a serious complication which results disastrously in a large percentage of cases, especially if it is not recognized during the operation. The left ureter is injured more frequently than the right during pelvic operations, incision being the most common type of ureteral accident. A ureterovaginal fistula is the usual sequel to ureteral injury. Although a normal ureter is never perforated by an ordinary ureteral catheter, this accident may occur if the ureteral wall has been injured by some preceding pathologic condition. The use of wire stylets should be abandoned. Operation is not necessarily required following perforation or rupture of the ureter.

In certain types of operation, such as hysterectomy for carcinoma, removal of large pelvic growths, and when difficulty is anticipated because of adhesions or other abnormal conditions, the insertion of ureteral catheters before operation is a time-saving procedure, aiding in the detection of the ureters and insuring them against injury.

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22. Higgins, C. C.: Aseptic Ureterointestinal Anastomosis, Am. J. Surg. **22**: 209 (Nov.) 1933.

23. Stevens, W. E.: Accidental Operative Injuries of the Female Ureter, J. Urol. **31**:741 (May) 1934.

(To be concluded.)

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